High incidence of hypertension-mediated organ damage in a series of Chinese patients with 17α-hydroxylase deficiency

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Abstract

Objective To analyze the prevalence of hypertension-mediated organ damage (HMOD) and its relationship with enzyme activity of mutant CYP17A1 and other risk factors in patients with 17α-hydroxylase/17,20-lyase deficiency (17-OHD).

Methods A total of 68 patients with 17-OHD were recruited in the Peking Union Medical College Hospital from 2003 to 2021. The incidence of hypertension and HMOD was respectively analyzed. CYP17A1 sequencing was performed and the enzyme activity of mutant CYP17A1 was determined by analyzing the characteristics of mutation itself and the functional data reported previously. A logistic regression model was employed to analyze the factors related to HMOD and the specific damaged organs in 17-OHD patients.

Result(s) Sixty-five patients (95.6%) exhibited hypertension, 32 of whom were diagnosed with HMOD. c.985_987del-TACinsAA (p.Y329KfsX418) (53.8%) and c.1459_1467del (p. del D487_F489) (11.4%) were the top two mutations, and no correlation was found between enzyme activity of mutant CYP17A1 and HMOD. The risk of HMOD increased by 32% for each additional year of hypertension duration, 10.2-fold for each one-grade increase in hypertension level, 2.3-fold for each grade of exacerbation of hypokalemia.

Conclusion Patients with 17-OHD experience a high incidence of HMOD. There was no correlation between the HMOD occurrence and enzyme activity of mutant CYP17A1. Longer duration of hypertension, more severe hypertension, and hypokalemia were independent risk factors for the occurrence of HMOD in patients with 17-OHD.

Keywords 17α-Hydroxylase/17,20-lyase deficiency · Hypertension · Hypertension-mediated organ damage

Introduction

In humans, P450c17 protein possesses activities of both 17α-hydroxylase and 17, 20-lyase, which are key enzymes for the biosynthesis of glucocorticoids and sex steroids [1–3]. 17α-hydroxylase converts pregnenolone and progesterone to 17α-hydroxyprogrenenolone and 17α-hydroxyprogesterone (17-OHP), respectively, and the latter two substances are further altered to the androgen precursors dehydroepiandrosterone and androstenedione by 17,20-lyase. CYP17A1 encodes P450c17 and biallelic mutations in CYP17A1 result in 17α-hydroxylase/17,20-lyase deficiency (17-OHD), in which the glucocorticoid and/or sex hormone synthesis pathway is blocked [4].

The lack of adrenal 17-hydroxylase activity forces steroidogenesis to corticosterone via 11-deoxycorticosterone (DOC), which in humans is a very minor adrenal product and less potent than aldosterone. Thus, the excess DOC results in sodium retention and hypokalemia. When the sex hormone synthesis pathway is blocked, androgen insufficiency arrests the development of testes in men with 46, XY karyotype at an early stage, and the normal internal genital ducts and external genitalia cannot be formed. In women with 46, XX karyotype, the decrease in estrogen synthesis prevents puberty and results in primary amenorrhea [5, 6].
Consequently, low-renin hypertension, hypokalemia, female infantilism, primary amenorrhea, and male pseudohermaphroditism are the typical clinical features of 17-OHD [1]. In the early stage, patients with 17-OHD often do not seek treatment owing to the lack of clinical manifestations and later consult the doctor for hypertension, hypokalemia, and sexual development abnormality [7, 8].

Hypertension-mediated organ damage (HMOD), previously termed as “target organ damage”, refers to structural or functional changes in arteries or end organs (i.e., heart, brain, retina, kidney, and blood vessels) [9, 10]. Early diagnosis is difficult, uncontrolled or poorly controlled HMOD significantly exacerbates the risk of end-organ damage [11–13]. Effective blood pressure lowering therapy can delay the progression of HMOD or even reverse it. Therefore, early identification of the condition and effective control of blood pressure is extremely important and meaningful [14–16]. Hypertension is a coexisting problem in nearly 95% of the 17-OHD patients [7]. It has been reported that 88% of the 17-OHD cases are not diagnosed accurately until puberty or even later due to its extremely low incidence and varied clinical phenotypes [8]. Accordingly, some 17-OHD patients may develop HMOD because of poor blood pressure control and inappropriate disease management.

In this study, we retrospectively analyzed the occurrence of HMOD and its relationship with enzyme activity of mutant CYP17A1 and other risk factors in 68 patients with 17α-hydroxylase/17,20-lyase deficiency (17-OHD) to augment our understanding of this rare disease.

**Subjects and methods**

**Subjects**

A total of 68 Chinese patients with 17-OHD who were admitted to the Peking Union Medical College Hospital (Beijing) were recruited for this study between 2003 and 2021.

The inclusion criteria [5, 17, 18] for subjects with 17-OHD were based on the clinical manifestations and serum hormone levels as follows: 1. low cortisol level and high ACTH level, high gonadotropins, high progesterone (P), and low testosterone (T) or estradiol (E2). 2. Patients aged ≥18 years at the clinical assessment.

This study was approved by the Ethics Committee for Human Research of Peking Union Medical College Hospital (No. JS-2111), and informed consents were obtained from all subjects participating in the study.

**Study design**

This was a retrospective study. Detailed medical data pertaining to age, sex, height, weight, the highest blood pressure ever measured, blood pressure at the function assessment of associated organs (heart, kidney, and retina), medication, hypertension duration (defined as the time span from the initial detection of hypertension to the assessment of HMOD) and imaging results (adrenal computed tomography (CT), pelvic and inguinal ultrasonography (USG), non-invasive transthoracic echocardiogram and resting standard 12-lead electrocardiography) were collected and analyzed. Serum potassium (K⁺) and sodium (Na⁺), cortisol (F), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), progesterone (P), testosterone (T), 17α-hydroxyprogesterone (17-OHP), and plasma adrenocorticotropic hormone (ACTH) at baseline (without treatment) were extracted and analyzed. Previous medications, including types and duration of medication (the time of adherence to medication), were also collected and the effects of them on HMOD were analyzed.

**Laboratory test**

Plasma ACTH and serum cortisol at 8:00 am were measured by chemiluminescence immunoassay (Advia Centaur XP, Bayer). Serum LH, FSH, estradiol (E2), progesterone (P), and testosterone (T) were measured with chemiluminescence (ACS: 180; Automatic Chemiluminescence Systems, Bayer). 17-hydroxyprogesterone (17-OHP) concentrations were determined by radioimmunoassay (Active 17α-OHP Progesterone DSL-5000, DSL). All hormone indexes above were measured in the context of absent hormone replacement therapy or drug withdrawal. The intra and inter-assay coefficients of variation were 2.3% and 2.8% for LH, 3.9% and 4.5% for FSH, 5.6% and 6.6% for T, 6.7% and 8.2% for ACTH, 5.3% and 5.7% for cortisol, 3.9% and 5.6% for 17-OHP, respectively.

**PCR and sequencing of CYP17A1 gene**

Genomic deoxyribonucleic acid (DNA) from the peripheral blood leukocytes were obtained from all patients using a standard procedure (Omega Blood DNA Midi Kit, Omega Bio-Tek, USA). PCR combined with sequencing was employed to detect the mutations in all 8 exons and exon-intron boundaries of CYP17A1 gene, PCR primers were designed by the Oligo Primer Analysis Software (version 7.60, Molecular Biology Insights, Inc., USA) and amplification methods are described in Supplementary Table S1. PCR products were identified on 1.5% agarose gel electrophoresis and sent to the Beijing SinoGenoMas Company for purification and sequencing. The sequence was compared with the reference sequence NM_000102.4 of the CYP17A1 gene and NP_000093.1 of P450c17 protein through the NCBI website to ascertain the mutations.
The enzymatic activity assessment of different CYP17A1 mutants

The enzymatic activity corresponding to different mutations of CYP17A1 was assessed according to the mutation characteristics and the functional data reported by previous literature. The enzymatic activity of mutants caused by the variants seriously affecting the gene transcription and translation (e.g., small deletions/insertions, large deletions, nonsense mutation, frameshift mutation, and splicing mutation) was considered “Nil” (completely abrogating the P450c17 protein function). The enzymatic activity of mutations verified on the previous literature was recognized as “Nil” (enzymatic activity abolished completely) or partial activity (residual enzyme function remained).

Classification criteria for body-mass index, potassium grade, and hypertension grade

Body-mass index (BMI) was calculated as weight in kg divided by the square of height in meters, and was classified into the following categories: underweight (<18.5 kg/m²), normal (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²), and obese (≥28.0 kg/m²) [19].

The definitions of serum potassium grade were as follows: normal serum potassium: ≥3.5 mmol/L; mild hypokalemia: 3.0–3.5 mmol/L; moderate hypokalemia: 2.5–3.0 mmol/L; severe hypokalemia: <2.5 mmol/L [20–22].

The definitions of hypertension grades were as follows [9, 23]: Grade 1 (mild): SBP 140–159 and/or DBP 90–99; Grade 2 (moderate): SBP 160–179 and/or DBP 100–109; Grade 3 (severe): SBP ≥ 180 and/or DBP ≥ 110.

Classification and assessment of HMOD

HMOD mainly involves the following organs [9]: heart: left ventricular hypertrophy, atrial fibrillation and other arrhythmias, ischemic heart disease, and heart failure; kidney: proteinuria (decrease in albumin–creatinine ratio) and renal dysfunction (decreased estimated glomerular filtration rate); retina: retinal hemorrhages, microaneurysms, hard exudates, cotton wool spots, and papilledema detected by fundoscopy which were conducted and interpreted by experienced ophthalmologists.

The results of routine urine, renal function, electrocardiography, echocardiography, fundoscopy were obtained to evaluate the damage to the heart, kidney, retina organs.

Statistical analysis

SPSS (version 26, SPSS, IBM) statistical software package was used to analyze the data. A normality test was performed to determine whether the continuous variables conform to normal distribution. The normally distributed variables were represented as mean ± standard deviation, and the non-normally distributed variables were expressed as median (upper and lower quartiles) [M (Q1, Q3)]. Comparison between two groups was performed using independent *t*-test or Mann–Whitney *U* test. Enumeration variables were expressed as cases (n) and percentages and were compared by the Chi-square test or Fisher exact test. The risk factors for the occurrence of HMOD in patients with 17-OHD were analyzed by logistic univariate regression. Subsequently, variables associated with the HMOD outcome in the univariate analysis with values of *p* < 0.05 were candidates for the multivariate logistic regression model. There is a strong correlation (r = 0.826, *P* < 0.05) between age and hypertension duration, and from a clinical perspective, the hypertension duration is more correlated with the occurrence of HMOD than age. Therefore, this variable is included in the further analysis of the HMOD risk model instead of age. Logistic multivariate regression was employed to estimate the independent risk factors for the occurrence of HMOD and the specific damaged organs in the 17-OHD patients. *P*-value less than 0.05 was considered statistically significant.

Results

Mutation analysis for CYP17A1 gene

A total of 66 out of 68 patients were tested for CYP17A1 mutation and the other two patients refused the test (Table 1). The mutation c.985_987delTACinsAA (p. Y329KfsX418) in Exon6 was the most common one among the Chinese 17-OHD patients, accounting for 53.8% of the mutant alleles (71/132), followed by the mutation c.1459_1467del GACTCTTTC (p. del D487_F489) (11.4%, 15/132). The majority of patients showed compound heterozygote, while 25 patients were homozygote, of which 19 showed the c.985_987delTACinsAA (Y329KfsX418) homozygote, 4 showed the c.1459_1467del GACTCTTTC (D487_F489del) homozygote and 2 showed the other mutant homozygote, respectively. According to previous literature [18, 24–30], the enzymatic activity caused by different mutations is also listed herein.

The clinical characteristics of 17-OHD patients

Among the 68 patients with 17-OHD, 36(52.9%) had 46, XX karyotype, and 32(47.1%) had 46, XY karyotype. The levels of P, FSH, LH, and ACTH were higher than the upper normal range, while the levels of T, E2, 17-OHP, and serum-free cortisol were lower than the normal low range. There was no significant statistical difference in each index between the genetic male (46XY) and the genetic female (46XX)
group (Table 2). No uterine or ovarian structures were found on USG in patients with 46, XY karyotype, and 28 patients (87.5%) had undergone gonadectomy. Among the patients with 46, XX karyotype, 19(52.8%) showed “infantile uterus” or “primordial uterus” on pelvic USG, and 17 (47.2%) did not have obvious uterine and ovarian structures despite the fact that they had not undergone a prior hysterectomy or gonadectomy. Among the 68 patients with 17-OHD, 41 had

| Mutation | DNA level | Protein effect | Location | enzyme activitya | Alleles/patients |
|----------|-----------|----------------|----------|-----------------|------------------|
| (c.157_159c.160_162) del TTC | Del F (53/54) | Exon1 | 37% [24, 30] | 1/1 |
| c.245C>A | A82D | Exon1 | 3.5% [25] | 2/2 |
| c.286C>T | R96W | Exon1 | 5%–25% [24, 26] | 2/2 |
| c.297 + 2T>C | Intron1 | Nil | 3/2 |
| c.298 – 1G>A | Intron1 | Nil | 3/3 |
| c.302delC | T101IlsX102 | Exon2 | Nil | 1/1 |
| c.346 + 1G>T | Intron2 | Nil | 1/1 |
| c.347 – 1G>C | Intron2 | Nil | 1/1 |
| c.445G>A | E149K | Exon3 | ND | 1/1 |
| c.626T>G | L209P | Exon3 | ND | 1/1 |
| (c.662_666&c.666+7) del TGAAGGTGAGAT ins CCACCTGCTTCA | | | | |
| c.707T>G | V236G | Exon4 | Nil | 1/1 |
| c.775_776del AT | I259HfsX274 | Exon5 | Nil | 3/3 |
| c.932_936delITTAATGG | V311fsX330 | Exon5 | Nil | 1/1 |
| (c.973_979_976_978_979_981) del GAA | Del K (325/326/327) | Exon6 | Nil | 1/1 |
| c.985_987delITACinsAA | Y329KfsX418 | Exon6 | Nil | 71/52 |
| c.1039C>T | R347C | Exon6 | 13.6% [28] | 1/1 |
| c.1072C>T | R358X | Exon6 | Nil | 2/2 |
| c.1080_1081del GC>A | L361fsX418 | Exon6 | Nil | 1/1 |
| c.1082T→C | L361P | Exon6 | ND | 2/2 |
| c.1084C>T | R362C | Exon6 | Nil [18, 24] | 1/1 |
| c.1085G>A | R362H | Exon6 | Nil [27] | 1/1 |
| c.1117delC | H373TfsX418 | Exon6 | Nil | 1/1 |
| c.1118A>T | H373L | Exon6 | Nil [24, 29] | 2/2 |
| c.1181_1183del TCA | del N (394) | Exon7 | Nil | 1/1 |
| c.1193C>T | A398V | Exon7 | ND | 1/1 |
| c.1217G>A | W406X | Exon7 | Nil | 1/1 |
| c.1221insA | H407QfsX415 | Exon7 | Nil | 1/1 |
| c.1226C>G | P409R | Exon7 | Nil [24] | 2/1 |
| c.1247G>A | R416H | Exon8 | Nil [24] | 1/1 |
| c.1253T>A | L418X | Exon8 | Nil | 1/1 |
| c.1459_1467del GACTCTTTC | del D487_F489 | Exon8 | Nil | 15/11 |
| c.1466del T | F489SfsX491 | Exon8 | Nil | 1/1 |
| c.1486T>C | R496C | Exon8 | <10% [24] | 1/1 |
| c.1497G>A | W499X | Exon8 | Nil | 1/1 |

a: From references, ND Not determined, Nil: Complete deficiency of CYP17A1
undergone adrenal CT scan, and 39 (95.1%) of them exhibited unilateral or bilateral thickened adrenal glands.

**Comparison of clinical characteristics of 17-OHD patients in the HMOD and non-HMOD groups**

The age of the patients, hypertension duration, blood pressure grade and hypokalemia grade in the HMOD group were higher than that of the non-HMOD group ($p < 0.05$). There was no statistically significant difference in other variables between the two groups (Table 3).

Regarding the medication, there was no statistical difference between the HMOD group and the non-HMOD group in the number of patients receiving antihypertensive agents or glucocorticoid, the medication duration, and medication types. Calcium channel antagonists were the most commonly used antihypertensive drugs, followed by angiotensin-aldosterone system inhibitors.

**The occurrence of hypertension and HMOD in 17-OHD patients**

Among the 68 patients with 17-OHD, 3 (4.4%) were normotensive and the remaining 65 (95.6%) were hypertensive. Among the patients with hypertension, 6 (9.2%) belonged to Grade 1, 21 (32.3%) to Grade 2, and 38 (58.5%) to Grade 3. After the diagnosis of hypertension, 23 patients (35.4%) did not regularly monitor their blood pressure or accept therapy at all, 17 (26.2%) received antihypertensive drugs alone to control blood pressure, 19 (29.2%) took

### Table 2 Clinical characteristics of 17-OHD patients

| Characteristics | 46XY ($n = 32$) | 46XX ($n = 36$) | $P$ |
|-----------------|----------------|----------------|-----|
| Age at the assessment (year) | 23.00 (19.00, 26.50) | 25.50 (20.25, 28.75) | 0.204 |
| Hypertension duration (year)$^a$ | 4.00 (2.00, 6.75) | 5.00 (2.00, 10.75) | 0.351 |
| BMI categories | | | |
| Normal weight | 13 | 19 | 0.341 |
| Overweight | 19 | 17 | |
| Hypertension grade$^*$ | | | |
| Normal potassium | 8 | 9 | 0.183 |
| Mild hypokalemia | 11 | 6 | |
| Moderate hypokalemia | 5 | 6 | |
| Severe hypokalemia | 8 | 16 | |
| Sodium (mmol/L)$^b$ | 140.00 (139.00, 141.75) | 141.00 (139.00, 143.00) | 0.358 |
| Potassium (mmol/L)$^b$ | 3.18 (2.48, 3.45) | 2.75 (2.20, 3.55) | 0.377 |
| 17-OHP (ng/ml) | 0.28 (0.12, 0.74) | 0.40 (0.20, 0.78) | 0.261 |
| P (ng/ml) | 9.33 ± 5.88 | 10.31 ± 5.89 | 0.534 |
| E2 (pg/ml) | 12.01 (4.40, 19.83) | 13.84 (6.85, 24.05) | 0.400 |
| T (ng/ml) | 0.09 (0.26) | 0.06 (0.22) | 0.589 |
| FSH (IU/L)$^*$ | 74.33 (51.45, 116.81) | 69.55 (31.67, 89.46) | 0.161 |
| LH (IU/L)$^*$ | 32.91 (22.85, 53.88) | 27.77 (20.75, 38.05) | 0.067 |
| ACTH (pg/mL)$^b$ | 137.30 (75.95, 274.00) | 122.00 (82.45, 193.00) | 0.572 |
| F (μg/dl)$^b$ | 0.63 (0.32, 1.10) | 0.95 (0.45, 1.73) | 0.182 |

Normal range: Sodium: 135–145 mmol/L, Potassium: 3.5–5.5 mmol/L, ACTH: 0–46 pg/ml, F: 4–22.3μg/dl, 17-OHP: 0.31–2.17 (Male); 0.10–0.80 ng/ml (Female); P: 0.10–0.84 ng/ml (Male), 0.38–2.28 ng/ml (Female); E2: <47 pg/ml (Male), 27–122 pg/ml (Female); T: 1.75–7.81 ng/ml (Male), 0.10–0.75 ng/ml (Female); FSH: 1.28–19.26 IU/L (Male), < 10 IU/L (Female); LH: 1.24–8.62IU/L (Male), 2.12–10.89IU/L (Female)

Abbreviation: 17-OHP: 17-hydroxyprogesterone, T Testosterone, P Progesterone, E2 Estradiol, FSH Follicle-stimulating hormone, LH Luteinizing hormone, ACTH Adrenocorticotropic hormone, F Cortisol

$^a$Plasma ACTH and cortisol concentrations were measured at 8 a.m.

$^b$The potassium grade and hypertension grade were classified according to the most severe hypertension and the lowest potassium concentration ever measured or tested

$^*$Hypertension duration refers to the time span from the initial detection of hypertension to the assessment of HMOD

$^b$The value of potassium concentration and sodium concentration corresponding to the most severe hypokalemia
glucocorticoids combined with antihypertensive drugs to control their blood pressure, including 9 (13.8%) patients who could not achieve well-controlled blood pressure with antihypertensive drugs alone until they were administrated with glucocorticoids. Moreover, 6 (9.2%) patients could bring their blood pressure to normal levels with glucocorticoid monotherapy (Fig. 1). Among the 17-OHD patients, 32 were identified to have HMOD (32/68, 47.1%), while the remaining 36 did not have HMOD (36/68, 52.9%) (Table 4). In the HMOD group, three patients had three organs damage, 14 had two organs damage, and 15 had one organ damage (Table 4). The kidney and the eyes were the most frequently affected organs, with more than half of the patients (56.3% and 68.8%, respectively) in the HMOD group suffering from the dysfunction of these two organs.

Table 3Comparison of clinical characteristics and laboratory indicators of 17-OHD patients between HMOD group and non-HMOD group

| Characteristics                              | HMOD group (n = 32) | NO HMOD group (n = 36) | P   |
|----------------------------------------------|--------------------|------------------------|-----|
| Age at the assessment (year)                 | 26.00 (24.00, 30.00)| 20.50 (19.00, 25.00)   | <0.001|
| Hypertension duration*                       | 8.50 (2.50, 12.00)  | 3.50 (0.25, 5.75)      | <0.001|
| BMI categories                               |                    |                        |     |
| Normal weight                                | 15                 | 17                     | 1.000 |
| Overweight                                   | 17                 | 19                     |       |
| Hypertension grade*                          |                    |                        | <0.001|
| Normotensive                                 | 0                  | 3                      |       |
| Grade 1                                      | 0                  | 6                      |       |
| Grade 2                                      | 4                  | 17                     |       |
| Grade 3                                      | 28                 | 10                     |       |
| Hypokalemia grade*                           |                    |                        | <0.001|
| Normal potassium                             | 0                  | 17                     |       |
| Mild hypokalemia                             | 6                  | 10                     |       |
| Moderate hypokalemia                         | 8                  | 3                      |       |
| Severe hypokalemia                           | 18                 | 6                      |       |
| 17-OHP (ng/ml)                               | 0.32 (0.16, 0.72)  | 0.46 (0.16, 0.82)      | 0.422 |
| P (ng/ml)                                    | 8.95 ± 5.40        | 10.65 ± 7.16           | 0.280 |
| E2 (pg/ml)                                   | 10.01 (4.67, 24.93)| 12.95 (7.40, 19.83)    | 0.676 |
| T (ng/ml)                                    | 0.06 (0.19)        | 0.09 (0.01, 0.28)      | 0.449 |
| FSH (IU/L)                                   | 76.80 (60.90, 99.38)| 56.15 (25.22, 99.86)  | 0.102 |
| LH (IU/L)                                    | 29.83 (22.85, 38.83)| 31.87 (17.89, 48.51)  | 0.867 |
| ACTH (pg/mL)                                 | 128.55 (86.18, 228.50)| 129.80 (75.08, 271.50)| 0.712 |
| F (μg/dl)                                    | 0.80 (0.46, 1.19)  | 0.71 (0.33, 1.82)      | 0.959 |
| SBP (mmHg)*                                  | 168.84 ± 19.37     | 157.44 ± 19.66         | 0.019 |
| DBP (mmHg)*                                  | 115.44 ± 12.44     | 103.19 ± 19.48         | <0.001|
| Potassium (nmol/L)*                          | 2.43 ± 0.61        | 3.39 ± 0.77            | <0.001|
| Sodium (mmol/L)*                             | 140.00 (139.00, 143.00)| 140.50 (139.00, 142.00)| 0.660 |
| SBP (mmHg)*                                  | 145.66 ± 6.17      | 143.22 ± 11.16         | 0.264 |
| DBP (mmHg)*                                  | 88.25 ± 10.81      | 87.42 ± 8.60           | 0.725 |
| Potassium (nmol/L)*                          | 3.42 ± 0.37        | 3.52 ± 0.43            | 0.295 |
| Medication intervention (number of hypertensive patients)* | 20 (32) | 22 (33) | 0.798 |
| Medication duration (year)*                  | 1.50 (0.50,4.75)   | 4.00 (0.50, 6.00)      | 0.312 |
| Patients number with residual enzyme activity* | 2                  | 5                      | 0.196 |

*The potassium grade and the hypertension grade were classified respectively according to the most severe hypertension and the lowest potassium concentration ever measured or tested

*aHypertension duration refers to the time span from the initial detection of hypertension to the assessment of HMOD

*bThe value of systolic blood pressure, diastolic blood pressure corresponding to the most severe hypertension

*cThe value of potassium concentration and sodium concentration corresponding to the most severe hypokalemia

*dThe systolic blood pressure, diastolic blood pressure, and potassium concentration at the assessment of HMOD

*eThe patients number receiving antihypertensive agents or glucocorticoid and the total number of hypertensive patients

*fMedication duration refers to the time length of regular medication therapy (antihypertensive agents or glucocorticoid)

#gThe number of patients with different residual enzyme activity, nil: enzymatic activity abolished completely, partial activity: residual enzyme function remained therapy
HMOD related risk factors in patients with 17-OHD

Hypertension duration, hypertension grade, and hypokalemia grade were the independent risk factors for HMOD in the patients with 17-OHD, as inferred from multivariate logistic regression analysis (Table 5). The risk of HMOD increased by 32% for each additional year of hypertension duration, 10.2-fold for each one-grade increase in hypertension level, 2.3-fold for each grade of exacerbation of hypokalemia.

We further analyzed the risk factors associated with specific organ damage in 17-OHD patients and found that the hypokalemia grade was the independent risk factor for both heart damage (Supplementary Table S2) and kidney damage (Supplementary Table S3), and the hypertension duration was the independent risk factors for retina (Supplementary Table S4).

Discussion

This study, for the first time, investigated the occurrence of HMOD in a large series of patients with 17-OHD from a single medical center. Our findings demonstrated that hypertension occurred in 95.6% of the patients with 17-OHD, 49.2% of whom had coexisting HMOD. The hypertension duration, hypertension grade, hypokalemia grade were the independent risk factors for HMOD in the patients.

From the perspective of pathogenesis, CYP17A1 gene mutation in the patients with 17-OHD resulted in the overproduction of aldosterone precursors such as DOC and corticosterone. Previous studies have shown that hyperaldosteronemia cannot only cause metabolic disorders and target organ damage by raising the blood pressure but also affect the blood vessels, myocardium, kidney, and other organs [31]. Whether DOC could cause damage to the relevant organs apart from its strong effect on the blood pressure remains to be investigated.

Searching the functional verification data of various CYP17A1 gene mutations in previous literature, we attempted to determine the relationship between the HMOD occurrence and the residual enzyme activity. Theoretically, the patients affected by mutations retaining partial enzyme activity tended to demonstrate milder clinical phenotypes and lesser risk of HMOD. We could not reach this conclusion possibly because most 17-OHD patients were confirmed to have complete combined 17-hydroxylase/17,20-lyase deficiency by genetic testing, where the mutations nearly abolished all the enzymatic activity, and the accessible mutations retaining partial enzyme activity were too few (6/132, 4.5%) to show any statistical difference.

Previous studies on the incidence of target organ damage in the Chinese population with essential hypertension have shown that severe hypertension (Grade 3) is an independent risk factor for damage to the heart, brain, kidney, and other organs [32]. Another study has revealed that 24 h systolic blood pressure is a major determinant of target organ damage irrespective of age and target organ, whereas 24 h diastolic blood pressure is only associated with kidney damage below middle age [33]. The hypertension grade is a stratified index based on the values of systolic and diastolic blood pressure of the most severe hypertension ever found, which can reflect the severity of the disease. A previous investigation has shown that the severity of hypertension, represented by the hypertension grade, is an important risk factor for target organ damage [34]. We also found that a longer hypertension duration, which suggested the longer duration of damage to target organs by hypertension, is a risk for HMOD. Therefore, patients with 17-OHD who have a higher hypertension grade and longer duration tend to have a higher risk for HMOD.

The main physiological functions of serum potassium are maintaining cell metabolism, regulating the osmotic pressure and acid-base balance, and supporting neuromuscular stress and normal functioning of the myocardium. Severe hypokalemia may present with somnolence, coma, and other nervous system manifestations. Besides, the condition can contribute to degeneration and necrosis of renal tubular epithelial cells, further leading to decreased function of urine concentration and hypokalemic nephropathy [35, 36]. Furthermore, hypokalemia can directly cause extremely dangerous ventricular fibrillation and cardiac arrest [37, 38]. In this study, hypokalemia grade classified according to the lowest potassium concentration ever tested was found to be an independent risk factor for HMOD in patients with 17-OHD. In addition to the fact that hypokalemia per se can affect the functioning of various organs, the degree of
hypokalemia depends on the overproduction of mineralocorticoids and can indicate the severity of 17-OHD. The lowering of serum potassium is the outcome of a serious loss of the enzymatic function of P450C17 and usually implies a high severity of the disorder. Therefore, hypokalemia is of definite clinical significance in the evaluation of HMOD induced by 17-OHD.

We found that among the patients with 17-OHD, between the initial diagnosis of hypertension and the assessment of HMOD, 35.4% of the hypertensive subjects did not regularly receive any medication therapy at all and that 64.6% were administrated antihypertensive drugs alone, glucocorticoid combined with antihypertensive drugs, or glucocorticoid alone to control their blood pressure. As hypertension in patients with 17-OHD is caused by the overproduction of mineralocorticoids (DOC, corticosterone) owning to the blockage of glucocorticoid synthesis, timely replacement therapy with corticosteroids can effectively inhibit the excessive secretion of ACTH and alleviate the accumulation of precursor substances (i.e., progesterone and pregnenolone). Hypertension can be relieved or even normalized in a majority of the patients with 17-OHD.

### Table 4 Clinical manifestations of 32 17-OHD patients with HMOD

| Patients no. | karyotype | Age (year) | SBP | DBP | Grade$^a$ | HMOD related organ damage |
|--------------|-----------|------------|-----|-----|----------|--------------------------|
| 6            | 46XY      | 18         | 170 | 130 | 3        | CKD, RP                  |
| 25           | 46XY      | 20         | 200 | 160 | 3        | ALB, RP                  |
| 31           | 46XY      | 25         | 180 | 100 | 3        | LVH                      |
| 33           | 46XY      | 22         | 170 | 120 | 3        | LVH, CKD                 |
| 35           | 46XY      | 23         | 210 | 140 | 3        | LVH                      |
| 36           | 46XY      | 24         | 150 | 100 | 2        | LVH, CHF                 |
| 40           | 46XY      | 28         | 160 | 110 | 3        | CKD, RP                  |
| 41           | 46XY      | 29         | 190 | 140 | 3        | LVH, RP                  |
| 42           | 46XY      | 30         | 140 | 100 | 2        | ALB, RP                  |
| 43           | 46XY      | 45         | 130 | 105 | 2        | ALB, RP                  |
| 44           | 46XY      | 59         | 170 | 110 | 3        | LVH, CKD                 |
| 47           | 46XX      | 18         | 150 | 100 | 2        | LVH, ALB                 |
| 49           | 46XX      | 26         | 170 | 110 | 3        | ALB                      |
| 51           | 46XX      | 18         | 180 | 120 | 3        | CKD                      |
| 55           | 46XX      | 24         | 175 | 110 | 3        | CKD                      |
| 61           | 46XX      | 30         | 160 | 110 | 3        | RP                       |
| 65           | 46XX      | 23         | 190 | 120 | 3        | LVH, CKD                 |
| 66           | 46XX      | 25         | 160 | 120 | 3        | PKD, RP                  |
| 67           | 46XX      | 25         | 150 | 115 | 3        | CKD, RP                  |
| 69           | 46XX      | 25         | 160 | 120 | 3        | LVH, CRF                 |
| 71           | 46XX      | 25         | 140 | 110 | 3        | RP                       |
| 72           | 46XX      | 26         | 180 | 110 | 3        | CKD                      |
| 75           | 46XX      | 26         | 158 | 118 | 3        | ALB, RP                  |
| 76           | 46XX      | 26         | 150 | 110 | 3        | RP                       |
| 77           | 46XX      | 27         | 200 | 150 | 3        | LVH                      |
| 79           | 46XX      | 28         | 180 | 130 | 3        | CKD, RP                  |
| 80           | 46XX      | 29         | 180 | 110 | 3        | PKD, RP                  |
| 83           | 46XX      | 35         | 170 | 110 | 3        | CKD, RP                  |
| 84           | 46XX      | 32         | 140 | 110 | 3        | RP                       |
| 85           | 46XX      | 32         | 170 | 120 | 3        | LVH                      |
| 86           | 46XX      | 37         | 190 | 110 | 3        | ALB, RP                  |
| 87           | 46XX      | 37         | 180 | 115 | 3        | ALB, RP                  |

$^a$hypertension grade

**ALB** Albuminuria; **CKD** Chronic kidney disease; **CRF** Chronic renal failure; **LVH** Left ventricular hypertrophy; **CHF** Chronic heart failure; **SBP** Systolic blood pressure; **DBP** Diastolic blood pressure; **IS** Ischemic stroke; **HS** Hemorrhagic stroke; **RP** Retinopathy
In our study, blood pressure control could not be achieved in nine hypertensive patients (13.8%) who were treated with antihypertensive drugs alone until they were administrated with glucocorticoids, whereas the blood pressure was controlled in 6 patients (9.2%) with glucocorticoid mono-therapy. These results indicate that addressing the etiology is very important in controlling the blood pressure of the patients. Our study suggests that the blood pressure management status of the 17-OHD patients is not optimistic and warrants much more attention and standardized treatment.

In our study, blood pressure control could not be achieved in nine hypertensive patients (13.8%) who were treated with antihypertensive drugs alone until they were administrated with glucocorticoids, whereas the blood pressure was controlled in 6 patients (9.2%) with glucocorticoid monotherapy. These results indicate that addressing the etiology is very important in controlling the blood pressure of the patients. Our study suggests that the blood pressure management status of the 17-OHD patients is not optimistic and warrants much more attention and standardized treatment.

In our study, there was no statistical difference between the HMOD group and the non-HMOD group in the number of patients receiving antihypertensive agents and glucocorticoids, the medication duration, and medication types. Consequently, we could not prove the beneficial effect of medication intervention on the prevention of HMOD. There may be two reasons. First, nearly two-thirds of hypertensive patients in both the HMOD and the non-HMOD groups had received antihypertensive agents or glucocorticoids to lower blood pressure levels. Second, the blood pressure of the patients in both groups was not controlled to the normal range before the assessment of HMOD. According to the previous studies, the organ condition of some patients with untreated essential hypertension who have preexisting HMOD can be improved if their blood pressure is maintained within the normal range for 3 years [16]. As for patients with 17-OHD, long-term follow-up and in-depth studies are needed to determine if achieving blood pressure control could improve the occurrence and development of HMOD.

**Limitations**

There are some limitations to this research. First, this was a retrospective study; hence, the medical information, including the initial clinical manifestations of 17-OHD and the relevant HMOD might have been affected by recall bias. Furthermore, there is a possibility of missing data due to

**Table 5 Risk factors associated with HMOD in 17-OHD patients**

| Factor                           | Logistic univariate regression OR (95% CI) | P   | Logistic multivariate regression OR (95% CI) | P   |
|----------------------------------|-------------------------------------------|-----|---------------------------------------------|-----|
| Hypertension duration (year)*    | 1.296 (1.118, 1.504)                      | 0.001 | 1.316 (1.060, 1.634)                      | 0.013 |
| BMI categories                   | 1.014 (0.391, 2.633)                      | 0.977 |                                             |      |
| Hypertension grade*              | 12.915 (3.731, 44.706)                    | <0.001 | 11.196 (2.153, 58.213)                     | 0.004 |
| Hypokalemia grade*               | 3.487 (1.983, 6.131)                      | <0.001 | 3.305 (1.494, 7.309)                       | 0.003 |
| 17OHP (ng/ml)                    | 0.514 (0.170, 1.556)                      | 0.239 |                                             |      |
| T (ng/ml)                        | 0.647 (0.106, 3.940)                      | 0.636 |                                             |      |
| P (pg/ml)                        | 0.958 (0.887, 1.035)                      | 0.278 |                                             |      |
| E2 (pg/ml)                       | 0.996 (0.965, 1.028)                      | 0.793 |                                             |      |
| FSH (IU/L)                       | 1.007 (0.996, 1.019)                      | 0.219 |                                             |      |
| LH (IU/L)                        | 0.990 (0.964, 1.017)                      | 0.473 |                                             |      |
| ACTH (pg/mL)                     | 1.000 (0.996, 1.004)                      | 0.894 |                                             |      |
| F(μg/dl)                         | 0.816 (0.606, 1.099)                      | 0.181 |                                             |      |
| Potassium (mmol/L)*              | 0.520 (0.154, 1.754)                      | 0.291 |                                             |      |
| SBP (mmHg)*                      | 1.030 (0.976, 1.087)                      | 0.275 |                                             |      |
| DBP (mmHg)*                      | 1.009 (0.960, 1.061)                      | 0.720 |                                             |      |
| Medication intervention*         | 0.833 (0.301, 2.706)                      | 0.726 |                                             |      |
| Medication duration (year)*      | 1.018 (0.937, 1.105)                      | 0.679 |                                             |      |
| Enzyme activity*                 | 0.186 (0.020, 1.697)                      | 0.136 |                                             |      |

*The potassium grade and the hypertension grade were classified respectively according to the most severe hypertension and the lowest potassium concentration ever measured or tested

Hypertension duration refers to the time span from the initial detection of hypertension to the assessment of HMOD

The systolic blood pressure, diastolic blood pressure, and potassium concentration at the assessment of HMOD

The patients number receiving antihypertensive agents and the total number of hypertensive patients

The patients number with different residual enzyme activity
previous limited examination conditions and uncontrollable patient willingness, for example, the lack of assessment of damage to the brain and the great vessels. These factors might have resulted in an underestimation of the incidence of HMOD in the patients with 17-OHD. Second, since most patients were not tested for DOC, the DOC level was not included in the analysis of factors associated with hypertension and HMOD, which may have further led to the incomplete analysis of the related risk factors for hypertension and HMOD in 17-OHD patients.

**Conclusion**

Taken together, hypertension is a common clinical manifestation of 17-OHD, patients with 17-OHD have a high incidence of HMOD. There was no correlation between the HMOD occurrence and the enzyme activity of mutant CYP17A1. Longer duration of hypertension, more severe hypertension, and hypokalemia were independent risk factors for the occurrence of HMOD in patients with 17-OHD.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no competing interests.

**Consent for publication** Written informed consent for publication of their clinical details and/or clinical images was obtained from all the patients or legal guardians participating in this study.

**Consent to participate** Written informed consent to participate in the study were obtained from all the participants or legal guardians participating in this study.

**Ethics approval** This study was approved by the Ethics Committee for Human Research of Peking Union Medical College Hospital (No. JS-2111), and informed consents were obtained from all subjects participating in the study.

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**References**

1. D. EL-Maouche, W. Arlt, D.P. Merke, Congenital adrenal hyperplasia. Lancet 390(10106), 2194–2210 (2017)
2. C.E. Kater, E.G. Biglieri, Disorders of steroid 17 alpha-hydroxylase deficiency. Endocrinol. Metab. Clin. North Am. 23 (2), 341–357 (1994)
3. W.L. Miller, R.J. Auchus, D.H. Geller, The regulation of 17,20-lyase activity. Steroids 62(1), 133–142 (1997)
4. B.C. Chung, J. Picado-Leonard, M. Haniu et al. Cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. Proc. Natl. Acad. Sci. U S A. 84(2), 407–411 (1987)
5. R.J. Auchus, Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J. Steroid. Biochem. Mol. Biol. 165 (Pt A), 71–78 (2017)
6. T. Yamase, E.R. Simpson, M.R. Waterman, 17 alpha-hydroxylase/17,20-lyase deficiency: from clinical investigation to molecular definition. Endocr. Rev. 12(1), 91–108 (1991)
7. R. Fontenele, M. Costa-Santos, C.E. Kater, 17alpha-hydroxylase deficiency is an underdiagnosed disease: high frequency of misdiagnoses in a large cohort of brazilian patients. Endocr. Pract. 24 (2), 170–178 (2018)
8. L. Hinz, D. Pacaud, G. Kline, Congenital adrenal hyperplasia causing hypertension: an illustrative review. J. Hum. Hypertens. 32(2), 150–157 (2018)
9. B. Williams, G. Mancia, W. Spiering et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur. Heart J. 39(33), 3021–3104 (2018)
10. Unger T., Borghi C., Charchar F. et al. 2020 International society of hypertension global hypertension practice guidelines. J. Hypertens. 38, 982–1004 (2020).
11. S.V. Greve, M.K. Blicher, T. Sehestedt et al. Effective risk stratification in patients with moderate cardiovascular risk using albuminuria and atherosclerotic plaques in the carotid arteries. J. Hypertens. 33(8), 1563–1570 (2015)
12. P. Perrone-Filardi, A. Coca, M. Galderisi et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the Euro. J. Hypertens. 35(9), 1727–1741 (2017)
13. B.H. Van Den Born, G.Y.H. Lip, J. Brugal-Huitj et al. ESC council on hypertension position document on the management of hypertensive emergencies. Eur. Heart J. Cardiovasc. Pharmacother. 5(1), 37–46 (2019)
14. G. De Simone, R.B. Devereux, R. Izzo et al. Lack of reduction of left ventricular mass in treated hypertension: the strong heart study. J. Am. Heart Assoc. 2(3), e00144 (2013)
15. M.T. Lonnebakken, R.Izzo, C.Mancusi, et al. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the Campania Salute Network). J. Am. Heart Assoc 6(3), e004152 (2017).
16. H. Triantafyllidi, D. Be Nas, A. Schoinas, et al. Hypertension-mediated organ damage regression associates with blood pressure variability improvement three years after successful treatment initiation in essential hypertension. J. Clin. Hypertens (Greenwich) 23(6), 1150–1158 (2021).
17. M. Zhang, S. Sun, Y. Liu et al. New, recurrent, and prevalent mutations: Clinical and molecular characterization of 26 Chinese patients with 17alpha-hydroxylase/17,20-lyase deficiency. J. Steroid Biochem. Mol. Biol. 150, 11–16 (2015)
18. C.S. Marivania, C.E. Kater, R.J. Auchus, Two prevalent CYP17 mutations and genotype-phenotype correlations in 24 Brazilian
patients with 17-Hydroxylase deficiency. J. Clin. Endocrinol. Metabol. 1, 49–60 (2004)
19. X. Zhang, M. Zhang, Z. Zhao et al. Geographic variation in prevalence of adult obesity in China: results from the 2013–2014 national chronic disease and risk factor surveillance. Ann. Intern. Med. 172(4), 291–293 (2020)
20. F.J. Gennari, Hypokalemia. N. Engl. J. Med. 339(7), 451–458 (1998)
21. A.J. Viera, N. Wouk, Potassium disorders: hypokalemia and hyperkalemia. Am. Fam. Physician 92(6), 487–495 (2015)
22. J. Ashurst, S.R. Sergent, B.R. Sergent, Evidence-based management of potassium disorders in the emergency department. Emerg. Med. Pract. 18(11), 1–24 (2016)
23. Chinese Hypertension Prevention and Treatment Guidelines Revision Committee H U C, Cardiology Branch of Chinese Medical Association. Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revised Edition). Chin J. Cardiovasc Med. 24(1), 25 (2009).
24. C.A. Marsh, R.J. Auchus, Fertility in patients with genetic deficiencies of cytochrome P450c17 (CYP17A1): combined 17α-hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency. Fertil. Steril. 101(2), 317–322 (2014)
25. Y.P. Wang, J. Li, J.X. Li et al. Three novel CYP17A1 gene mutations (A82D, R125X, and C442R) found in combined 17α-hydroxylase/17,20-lyase deficiency. Metabolism 60(10), 1386–1391 (2011)
26. N. Laflamme, J.F. Leblanc, J. Mailloux et al. Mutation R96W in cytochrome P450c17 gene causes combined 17α-hydroxylase/17α-lyase deficiency in two French Canadian patients. J. Clin. Endocrinol. Metab. 81(1), 264–268 (1996)
27. N. Nájera, N. Garibay, Y. Pastrana et al. Loss of cytochrome P450 17A1 protein expression in a 17α-hydroxylase/17,20-lyase-deficient 46,XY female caused by two novel mutations in the CYP17A1 gene. Endocr. Pathol. 20(4), 249–255 (2009)
28. E.L. Van Den Akker, J.W. Koper, A.L. Boehmer et al. Differential inhibition of 17alpha-hydroxylase and 17,20-lyase activities by three novel missense CYP17 mutations identified in patients with P450c17 deficiency. J. Clin. Endocrinol. Metab. 87(12), 5714–5721 (2002)
29. Y.M. Kim, M. Kang, J.H. Choi et al. A review of the literature on common CYP17A1 mutations in adults with 17-hydroxylase/17,20-lyase deficiency, a case series of such mutations among Koreans and functional characteristics of a novel mutation. Metabolism 63(1), 42–49 (2014)
30. K. Miura, K. Yasuda, T. Yanase et al. Mutation of cytochrome P-450alpha gene (CYP17) in a Japanese patient previously reported as having glucocorticoid-responsive hyperaldosteronism: with a review of Japanese patients with mutations of CYP17. J. Clin. Endocrinol. Metab. 81(10), 3797–3801 (1996)
31. S. Ardhnanari, R. Kannuswamy, K. Chaudhary et al. Mineralocorticoid and apparent mineralocorticoid syndromes of secondary hypertension. Adv. Chronic. Kidney Dis. 22(3), 185–195 (2015)
32. H. Cui, F. Wang, L. Fan et al. Association factors of target organ damage: analysis of 17,682 elderly hypertensive patients in China. Chin Med. J. (Engl) 124(22), 3676–3681 (2011)
33. F.F. Wei, Y. Li, L. Zhang et al. Association of target organ damage with 24-hour systolic and diastolic blood pressure levels and hypertension subtypes in untreated Chinese. Hypertension 63(2), 222–228 (2014)
34. H.E. Nelissen, M.E. Hendriks, F.W.N.M. Wit et al. Target organ damage among hypertensive adults in rural Nigeria: a cross-sectional study. J. Hypertens. 32(3), 487–494 (2014)
35. S. Reungjui, C.A. Roncal, W. Sato et al. Hypokalemic nephropathy is associated with impaired angiogenesis. J. Am. Soc. Nephrol. 19(1), 125–134 (2008)
36. A.S. Relman, W.B. Schwartz, The kidney in potassium depletion. Am. J. Med. 24(5), 764–773 (1958)
37. T. Dyckner, Relation of cardiovascular disease to potassium and magnesium deficiencies. Am. J. Cardiol. 65(23), 44K–46K (1990)
38. B.F. Palmer, D.J. Clegg, Physiology and pathophysiology of potassium homeostasis. Adv. Physiol. Educ. 40(4), 480–490 (2016)