BMC Endocrine Disorders

RESEARCH

Open Access

Wilson disease combined with polycystic ovary syndrome–clinical features, treatment, and outcome in Chinese patients

Lin Chen[1], Ming-juan Fang[1], Liang-liang Zhang[1], Yong-feng Liu[1], Yong-zhu Han[1], Xu-en Yu[1*] and Yin Xu[1*]

Abstract

Objective We aimed to analyze the clinical features, treatment, and prognosis of Wilson disease (WD) combined with polycystic ovary syndrome (PCOS), and to explore the correlation between endocrine abnormalities and liver damage.

Patients and methods The clinical data of 40 female patients of WD combined with PCOS (PCOS-WD) were retrospectively analyzed. 43 age- and BMI-matched patients of PCOS with non-WD (PCOS-NWD) were performed as the control group. The patients of PCOS-WD were assigned to adolescent group ($n=18$) and reproductive age group ($n=22$) according to the age onset of PCOS, and also assigned to normal testosterone group ($n=18$) and elevated testosterone group ($n=22$) according to the testosterone level. The clinical features, laboratory tests, imaging examinations, treatment, and outcome of all patients were analyzed, and correlation analysis was processed between gonadal hormone and liver damage parameters.

Results The testosterone level was significantly higher in the PCOS-NWD than in the PCOS-WD patients (Z=-2.306, $P=0.021$). The clinical hyperandrogenism was significantly more prevalent in adolescent group within PCOS-WD patients ($P=0.025$), while the serum alanine aminotransferase was significantly higher in reproductive age group (Z=-2.572, $P=0.010$). The hepatic fibrosis index was significantly higher in elevated testosterone group than in normal testosterone group (Z = -2.190, $P=0.029$), while the progesterone level was lower in elevated testosterone group ($Z=2.394$, $P=0.017$). The testosterone level was positively correlated with the hepatic fibrosis index ($P=0.039$, $R=0.328$). In followed-up observations, no significant difference was found in menstrual cycle and pregnancy outcomes between progesterone combined with copper chelation therapy and copper chelation therapy alone.

Conclusion PCOS is an important endocrine comorbidity of female WD patients. The extent of liver damage in WD patients may be related to the hormonal imbalance of PCOS. The study recommends routine screening for PCOS in adolescent WD patients. Testosterone levels may serve as a valuable reference for informing treatment decisions. Copper chelation therapy with or without progesterone is beneficial to the recovery of patients with PCOS-WD.

Strengths and limitations of this study

1. Contributing to the expanded understanding of endocrine comorbidity in WD.

*Correspondence:
Xu-en Yu
yuxuen@ahtcm.edu.cn
Yin Xu
fmrixuy@126.com

Full list of author information is available at the end of the article

2. Emphasis copper chelation therapy is beneficial to the recovery of WD patients with comorbid PCOS.
3. The sample size was limited, and larger scale clinical cohort studies are needed to provide more conclusive evidence.
4. The large-sample multi-center observations of standard dosage courses are needed to confirm the treatment plan in the future.

Keywords Wilson disease, Endocrinologic abnormality, Polycystic ovary syndrome, Hyperandrogenism, Copper chelation therapy

Introduction

Wilson disease (WD) is an autosomal recessive disease caused by mutations in the ATP7B gene that encodes a copper-transporting ATPase [1]. As firstly described in detail by Kinnier Wilson in 1912 [2], WD was a rare multisystemic disorder caused by copper accumulation [3]. Although hepatic and neuropsychiatric symptoms are the typical clinical characteristics, patients with WD may frequently experience some under-recognized endocrine disorders that may hinder their qualities of life [4]. The disturbances of endocrine system are also involved in clinical manifestation of WD, which can lead to recurrent abortions, infertility, growth disruption, and parathyroid failure. In particular, female patients of WD are more prone to endocrine system involvement due to their natural physiological characteristics, such as menstruation, pregnancy, and childbearing. However, the female patients with endocrinologic abnormalities, especially polycystic ovary syndrome (PCOS), are rarely described as a comorbidity in patients with WD.

PCOS is the most common endocrinopathy in women of reproductive age, which characterized by hyperandrogenism, oligomenorrhea, polycystic ovary morphology, and insulin resistance [5, 6]. As a common reproductive disorder, PCOS also have significant implications for the menstruation, pregnancy outcomes and long-term health of the women [7, 8]. For the female patients of WD, infertility, anovulation, and amenorrhea often occurred according to previous studies [9]. Many of the untreated female patients with WD have primary amenorrhea, irregular menstruation, secondary amenorrhea, and the low probability of normal pregnancy [10, 11]. Also, recurrent abortions are more frequent in patients without effective treatment [12–14]. In short, although female patients of WD can present with various endocrine abnormalities, the detailed clinical features of WD combined with PCOS, especially in different age of onset or gonadal hormone levels, have not been mentioned.

Unlike regular PCOS patients, liver damage is rather universal in WD [15]. As for whether liver damage was related to the occurrence of PCOS, there was currently some controversy [16]. Some studies believe that the key features of PCOS have been implicated as factors that contribute to the development of nonalcoholic fatty liver disease [17], while others genetically predict that nonalcoholic fatty liver disease increases the risk of PCOS development [18]. Currently, the relationship between the liver damage and PCOS in patients with WD have not been investigated yet. In addition, female patients with WD presented with multiple endocrine manifestations could be easily ignored and inappropriately treated. Actually, it is entirely possible to become pregnant for females with mild hepatic/neuropsychiatric symptoms and adherence to regular treatment [19]. However, the treatment strategy and pregnancy outcome of WD with PCOS are still unknown.

In the present study, we aimed to explore the clinical features of WD combined with PCOS at different age of onset and gonadal hormone levels in our single-center compared to PCOS-NWD patients. The association of endocrine-metabolic abnormalities and liver damage was also focused. And, the appropriate treatment strategies and prognosis for the disease has also been emphasized. These data would contribute to expand the spectrum of endocrine involvement in WD. This study should be useful for counseling patients and for guiding the optimal management of rational treatment on the patients of WD with comorbid PCOS.

Materials and methods

Participants

The study included 40 hospitalized patients of WD with PCOS in the Affiliated Hospital of Institute of Neurology, Anhui University of Chinese Medicine. WD was diagnosed in accordance with the 2012 European Association for Study of the Liver Clinical Practice Guidelines [2]. PCOS was diagnosed in female patients in accordance with the criteria established by the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine international consensus working group (also known as the Rotterdam criteria). These criteria included hyperandrogenism (biochemical or clinical), irregular anovulatory cycles (> 35 days or < 21 days), and polycystic ovary morphology [5]. PCOS was divided into adolescence (≤ 18 years) and reproductive age (>18 years) based on the age of onset [20]. At least two of the above-mentioned three criteria must be met for PCOS diagnosis in the reproductive age, and three criteria must be met for PCOS diagnosis in adolescence.

All the 40 patients of WD were diagnosed to have PCOS (PCOS-WD). In addition, 43 age- and BMI-matched PCOS patients not combined with WD (PCOS-NWD) were selected in the outpatient of gynecology as the control group. This study was approved by the ethics committee of Anhui University of Chinese Medicine and all participants signed informed consent.

Laboratory tests and imaging examinations

Written consent was obtained for each patient for data processing and analysis. The medical records of the patients were examined to collect data regarding demographic characteristics, clinical manifestations, laboratory findings, imaging examinations, treatment, and prognosis. The serum parameters were estimated in each group, including serum lipid levels (triglyceride and cholesterol), serum glucose levels, and gonadal hormone concentrations (total testosterone level, prolactin level, progesterone level, luteinizing hormone level, follicle-stimulating hormone, the ratio of LH/FSH, estradiol). Ultrasound examination of the abdomen and ovary was also conducted for all the patients. The following parameters were estimated in the patients of PCOS-WD, including liver function parameters (serum alanine transaminase and aspartate aminotransferase levels), copper metabolism (serum copper and ceruloplasmin) and magnetic resonance imaging (MRI) of the brain. All examinations were performed with patient's consent.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA). Data analysis was performed using descriptive statistics; Fisher's exact test was used for categorical variables, while the Mann–Whitney *U* test was used for continuous variables. Spearman's correlation analysis was used to analyze the relationship between the gonadal hormone levels and liver metabolic parameters. A *P*-value of < 0.05 was considered statistically significant.

Table 1 Patients' demographic characteristics

Variable	PCOS-WD group(*N* = 40)	PCOS-NWD group(*N* = 43)	Z/χ^2	*P*
Age of PCOS onset	19.5(15–31)	20(15–30)	-0.229	0.819
≤ 18y	18/40	19/43	-	-
>18y	22/40	24/43	-	-
Age of menarche	13(11–15)	12(11–14)	2.880	**0.004**
BMI	22.35(14.5–38.3)	22.6(17.7–33.4)	-0.346	0.729
<24	24/40	27/43	-	-
≥ 24	8/40	10/43	-	-
≥ 28	8/40	6/43	-	-
Hyperandrogenism	17/40	19/43	0.000	1.000
Irregular menstruation	40/40	43/43	-	-
polycystic ovary morphology	40/40	43/43	-	-

Note: PCOS = polycystic ovary syndrome, PCOS-WD = polycystic ovary syndrome combined with Wilson disease, PCOS-NWD = polycystic ovary syndrome not combined with Wilson disease, BMI = Body Mass Index

Results

General characteristics of WD combined with PCOS

All the 40 female patients of WD were from China. The median age at onset of PCOS was 19.5 years (15–31 years), including abnormal menstruation (menolipsis, longer menstrual cycle, and hypomenorrhea) and hyperandrogenism (crinosity, obesity, and acne). The age at onset of hepatic/neuropsychiatric symptoms (median age:14.5 years) was younger than that of PCOS (median age:19.5 years), including neurologic symptoms (dystonia, tremor, and dysarthria), hepatic symptoms (lower limb edema, bloating, and jaundice), and psychiatric issues (anxiety, depression, and irritability). The median body mass index (BMI) was 22.35 (14.5–38.3), of which 8 patients (8/40) were overweight (BMI ≥ 24) and 8 patients (8/40) were obese (BMI ≥ 28). The remaining patients (24/40) had normal BMI (Table 1).

Group comparison between PCOS-WD and PCOS-NWD

The median age at onset of PCOS in PCOS-NWD group was 20 years (range: 15–30 years), and had no difference with PCOS-WD group. The median body mass index (BMI) was 22.6(17.7–33.4) in PCOS-NWD group, and also had no difference with PCOS-WD group (Table 1). Age of menarche was lower in patients of PCOS-NWD ($Z = 2.880$, $P = 0.004$) (Table 1). Testosterone levels were significantly higher in patients of PCOS-NWD (Z=-2.306, $P = 0.021$) (Table 2), while the clinical hyperandrogenism was found no difference between the two groups ($P = 1.000$) (Table 1). FSH was significantly higher in patients of PCOS-NWD (Z=-2.452, $P = 0.014$), and LH/FSH was significantly lower in patients of PCOS-NWD ($Z = 2.443$, $P = 0.015$) (Table 2). There was also no difference in prolactin, progesterone, LH, E2, glucose, TC, and TG between the two groups (Table 2). All patients in each groups exhibited oligomenorrhea or menopause, and the doppler ultrasound examination revealed polycystic ovary morphology changes (Fig. 1).

Intra-group comparison between adolescent group and reproductive age group in PCOS-WD

In view of the different characteristics in PCOS between adolescent and reproductive age, we conducted the subgroup analysis based on age of onset. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were significantly higher in the reproductive age group (Z=-2.572, $P = 0.010$; Z=-2.326, $P = 0.020$), as

Table 2 Laboratory data of PCOS-WD group vs. PCOS-NWD group

Parameter	Total ($n=83$) Median (IQR)	PCOS-WD group ($n=40$) vs. PCOS-NWD group ($n=43$)	
		Z	*P*
Testosterone	0.74(1.12)	-2.306	**0.021**
Prolactin	24.67(12.00)	-0.150	0.880
Progesterone	0.48(0.69)	-0.273	0.785
LH	11.6(8.84)	-1.221	0.222
FSH	6.47(2.71)	-2.452	**0.014**
LH/FSH	1.9(1.71)	2.443	**0.015**
E2	68.46(49.98)	-1.682	0.093
Glucose	4.96(0.76)	-1.773	0.076
TC	4.25(1.23)	-0.036	0.971
TG	0.98(0.51)	-1.705	0.088

Note: PCOS = polycystic ovary syndrome, PCOS-WD = polycystic ovary syndrome combined with Wilson disease, PCOS-NWD = polycystic ovary syndrome not combined with Wilson disease, IQR = Inter-Quartile Range, LH = luteinizing hormone, FSH = follicle-stimulating hormone, E2 = estradiol, TC = total cholesterol, TG = triglyceride

was the serum ceruloplasmin level (Z=-2.963, $P=0.003$) and the serum E2 (Z=-2.447, $P=0.014$) (Table 3). There was no significant difference between the two groups in testosterone, prolactin, luteinizing hormone, LH, FSH, LH/FSH, glucose, TC, TG, copper, and hepatic fibrosis index (HFi) (Table 3). The incidence of clinical hyperandrogenism was significantly increased in the adolescent group ($P=0.025$) (Table 4). No difference was found in the clinical symptoms including neurologic, hepatic, psychiatric, and menstrual abnormalities between the two subgroups, and also in imaging manifestations including cirrhosis, polycystic ovary morphology, and brain MRI abnormalities (Table 4).

Intra-group comparison between normal testosterone group and elevated testosterone group in PCOS-WD

In view of the importance of biochemical hyperandrogenism in the diagnosis of PCOS, we conducted a subgroup analysis according to androgen levels. The HFi was significantly higher in elevated testosterone group than in normal testosterone group (Z = -2.190, $P=0.029$). The progesterone level was lower in elevated

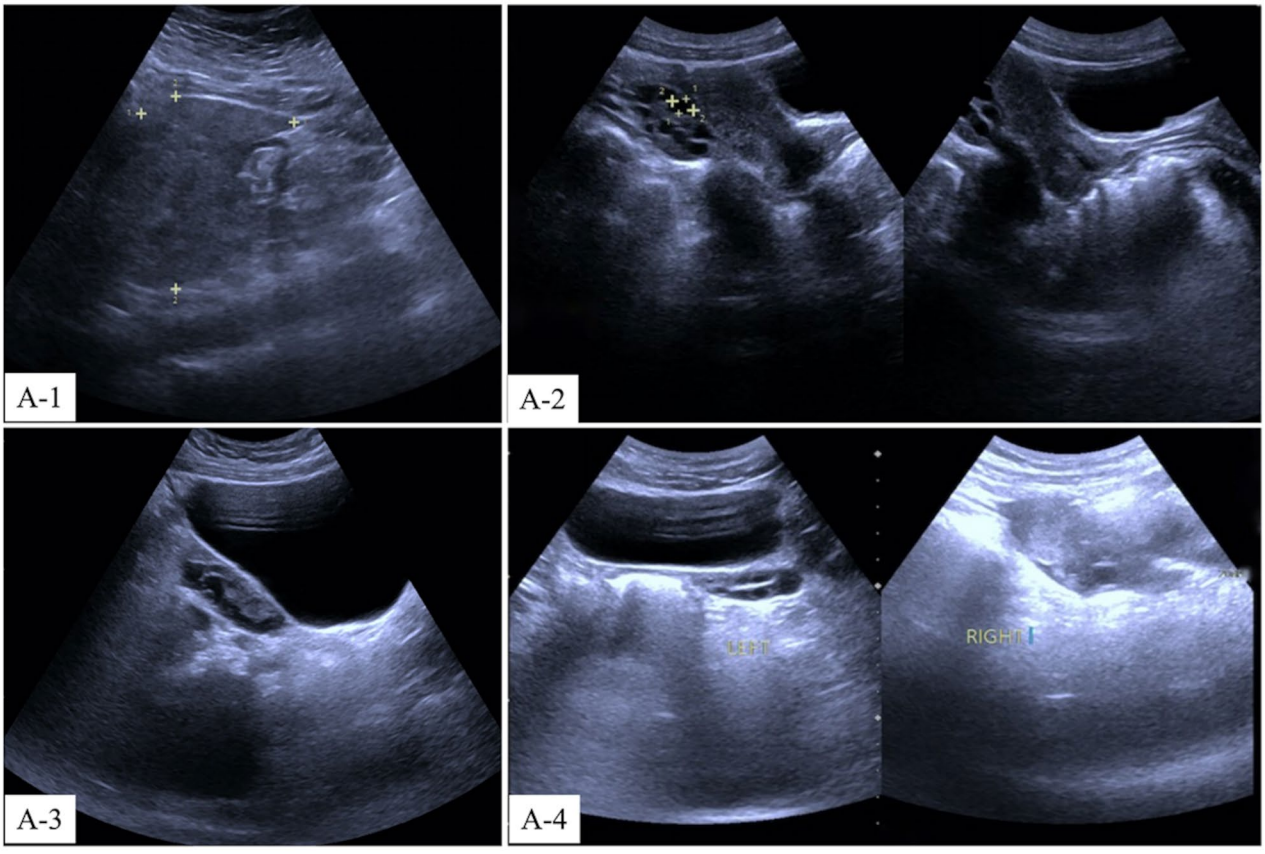

Fig. 1 Ultrasound examination of the ovary. **A-1**: Ovary ultrasound showed multiple anechoic area in bilateral ovaries, well-defined, maximum is about 8*7 mm (case 1). **A-2**: Ovary ultrasound showed multiple anechoic area, well-defined in bilateral ovaries, maximum 8*6 mm (case 3). **A-3**: Ovary ultrasound showed increased multiple anechoic areas in ovaries (case 6). **A-4**: Ovary ultrasound showed multiple anechoic area in bilateral ovaries, well-defined, maximum of the right side about 8*7 mm, the left side about 9*6 mm (case 8)

Table 3 Laboratory data of 40 WD patients comorbid with PCOS

Parameter	Total ($n=40$) Median (IQR)	Adolescent group ($n=18$) vs. Reproductive age group ($n=22$)		Normal testosterone group ($n=18$) vs. Elevated testosterone group ($n=22$)	
		Z	*P*	Z	*P*
Testosterone	0.59(0.77)	-0.163	0.870	-	-
Prolactin	24.6(13.31)	-0.517	0.605	-1.414	0.157
Progesterone	0.455(0.71)	-0.054	0.957	2.394	**0.017**
LH	12.715(10.69)	-1.196	0.232	-0.136	0.892
FSH	5.825(2.18)	-0.408	0.683	-1.414	0.157
LH/FSH	2.325(1.40)	-1.224	0.221	-1.441	0.150
E2	62.045(40.34)	-2.447	**0.014**	-0.054	0.957
Glucose	4.715(0.76)	-0.408	0.683	-0.068	0.946
TC	4.305(1.41)	-1.944	0.052	2.828	**0.005**
TG	0.865(0.47)	-0.326	0.744	-1.115	0.265
CP	48.55(34.7)	-2.963	**0.003**	-0.693	0.488
Copper	2.03(2.06)	-0.870	0.384	-0.082	0.935
ALT	27.00(24.00)	-2.572	**0.010**	-0.422	0.673
AST	27.00(23.00)	-2.326	**0.020**	-0.082	0.935
HFi	1.445(0.27)	-1.496	0.135	-2.190	**0.029**
Age of menarche	13.00(2.00)	-1.789	0.074	-0.873	0.383
BMI	22.35(8.1)	-0.517	0.605	-0.299	0.765

Note: PCOS = polycystic ovary syndrome, WD = Wilson disease, IQR = Inter-Quartile Range, ALT = alanine aminotransferase, AST = aspartate transaminase, TC = total cholesterol, TG = triglyceride, LH = luteinizing hormone, FSH = follicle-stimulating hormone, E2 = estradiol, CP = ceruloplasmin, HFi = hepatic fibrosis index, BMI = Body Mass Index

Table 4 The main clinical and imaging features of the 40 WD patients comorbid with PCOS

Clinical feature	Total ($n=40$)	Adolescent group ($n=18$)	Reproductive age group ($n=22$)	*p*	Normal level group($n=18$)	Elevated level group($n=22$)	*p*
Neurologic	32(80%)	14(77.8%)	18(81.8%)	1.000	14(77.8%)	18(81.8%)	1.000
Hepatic	40(100%)	18(100%)	22(100%)	-	18(100%)	22(100%)	-
Psychiatric	8(20%)	5(27.8%)	3(13.6%)	0.430	3(16.7%)	5(22.7%)	0.709
Irregular menstruation	40(100%)	18(100%)	22(100%)	-	18(100%)	22(100%)	-
Hyperandrogenism	20(50%)	13(72.2%)	7(31.8%)	**0.025**	9(50%)	11(50%)	1.000
Polycystic ovarian morphology	40(100%)	18(100%)	22(100%)	-	11(100%)	15(100%)	-
Liver cirrhosis	36(90%)	15(83.3%)	21(95.5%)	0.310	15(83.3%)	21(95.5%)	0.310
Brain MRI abnormality	31(77.5%)	13(72.2%)	18(81.8%)	0.705	13(72.2%)	18(81.8%)	0.705

Note: PCOS = polycystic ovary syndrome, WD = Wilson disease, MRI = magnetic resonance imaging. Data are expressed as n (%) or median (range) values. An ultrasound examination of the abdomen and ovary confirmed cirrhosis and polycystic ovary morphology, respectively

testosterone group ($Z=2.394$, $P=0.017$). The cholesterol level was significantly lower in the elevated testosterone group ($Z=2.828$, $P=0.005$) (Table 3). No significantly difference was found in clinical symptoms including neurologic, hepatic, psychiatric, menstrual abnormalities, and hyperandrogenism between the two subgroups, and also in imaging manifestations including cirrhosis, polycystic ovary morphology, and brain MRI abnormalities (Table 4).

Correlation analysis on liver damage and gonadal hormone levels in WD combined with PCOS

To explore the association on abnormal hormone levels and liver metabolism in WD, we analyzed the correlation between serum gonadal hormone levels (testosterone, prolactin, progesterone, LH, FSH, E2) and liver metabolic parameters (ALT, AST, copper metabolism, and hepatic fibrosis index). In the correlation analysis, HFi was positively correlated with serum testosterone level ($P=0.039$, $R=0.328$), and negatively correlated with progesterone ($P<0.05$, R = -0.3) and LH ($P<0.05$, R = -0.4). The AST level was negatively correlated with progesterone ($P<0.05$, R = -0.4) and LH ($P<0.05$, R = -0.3). The serum copper was positively correlated with prolactin ($P<0.05$, $R=0.3$) (Fig. 2).

Therapy and outcome of WD combined with PCOS

In the treatment of WD, D-Penicillamine was taken regularly in 57.5% of the patients and intermittently in 35% of the patients. Due to irregularity in taking copper

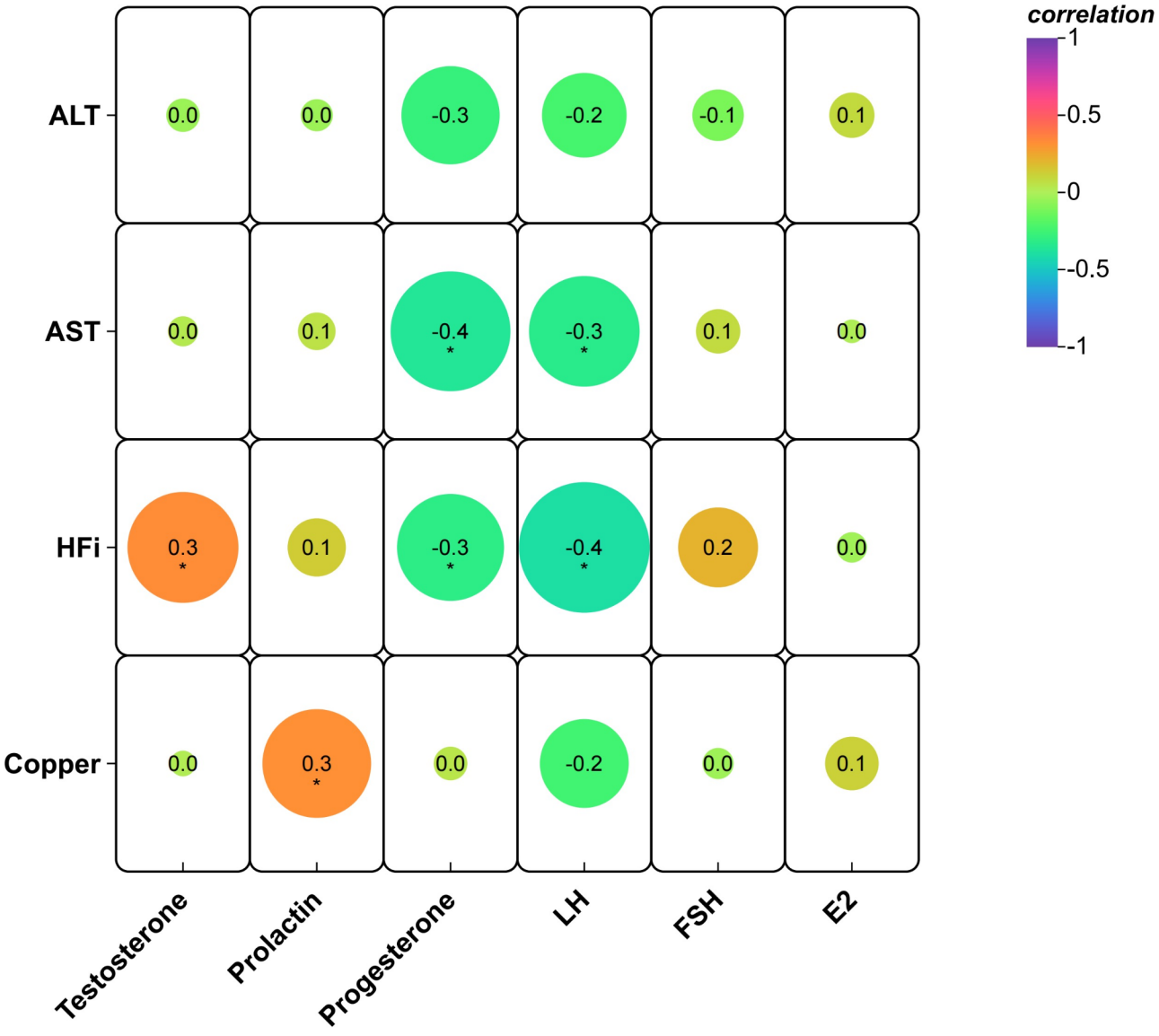

Fig. 2 Heatmap of Spearman's correlation between liver function and hormonal parameters. Warm colors indicate a positive correlation, in which the expression levels of liver function and hormonal tend to increase or decrease simultaneously. Cool colors represent a negative correlation, meaning that when the expression level of liver function increases, the level of hormonal decreases. The varying intensities of color reflect different degrees of correlation, with lighter shades representing weaker correlations and deeper shades indicating stronger correlations. The correlation coefficients range from − 1 to 1, with red near 1 indicating a very strong positive correlation and blue near − 1 indicating a very strong negative correlation. The numbers in the circle represent the correlation coefficient between liver function and hormonal. The asterisk indicates the *P*-value is less than 0.05, showing the statistical significance of the correlation. *ALT = alanine aminotransferase, AST = aspartate aminotransferase, Copper = serum copper level, HFi = hepatic fibrosis index, LH = luteinizing hormone, FSH = follicle-stimulating hormone, E2 = estradiol*

chelating drugs, five patients showed aggravation of cirrhosis, while three patients showed aggravation of torsion spasm. The remaining patients exhibited good recovery of their hepatic symptoms (23/40) and the neurologic restored (18/40) respectively (Table 5). In comparison of treatment and outcomes in subgroup, no statistically difference was found in subgroup based on different ages of onset or different testosterone levels (Table 5). While in the treatment of PCOS, only thirteen patients (32.5%) took progesterone in the course. In followed-up observations ranged from 3 to 57 months, no significant difference was found in menstrual cycle and pregnancy outcomes between progesterone combined with copper chelation therapy and copper chelation therapy alone (Table 6).

Discussion

Based on the present study, we systematically evaluated the clinical features, treatment, and outcome on 40 patients of WD combined with PCOS. Clinical features

Table 5 Therapy and outcome of 40 patients WD comorbid with PCOS

Therapy and Outcome	Total (*n* = 40)	Adolescent group (*n* = 18)	Reproductive age group (*n* = 22)	*p*	Normal level group(*n* = 18)	Elevated level group(*n* = 22)	*p*
WD therapy							
-D-penicillamine	23(57.5%)	10(55.6%)	13(59.1%)	1.000	10(55.6%)	13(59.1%)	1.000
-zinc	35(87.5%)	17(94.4%)	18(81.8%)	0.355	15(83.3%)	20(90.9%)	0.642
-Intermittent medication	14(35%)	6(33.3%)	8(36.3%)	1.000	6(33.3%)	8(36.3%)	1.000
PCOS therapy							
-progesterone	13(32.5%)	4(22.2%)	9(40.9%)	0.312	5(27.8%)	8(36.4%)	0.737
Outcome (WD)							
-Hepatic restored	23(57.5%)	11(61.1%)	12(54.5%)	0.755	9(50%)	14(63.6%)	0.523
-Neurologic restored	18(45%)	8(44.4%)	10(45.4%)	1.000	9(50%)	9(40.9%)	0.750
Outcome (PCOS)							
-Menstruation restored	26(65%)	13(72.2%)	13(59.1%)	0.510	11(61.1%)	15(68.2%)	0.744
-Pregnancy	5(12.5%)	2(11.1%)	3(13.6%)	1.000	3(16.7%)	2(9.1%)	0.642
-Spontaneous abortion	3(7.5%)	2(11.1%)	1(4.5%)	0.579	2(11.1%)	1(4.5%)	0.579
-Procreation	3(7.5%)	1(5.6%)	2(9.1%)	1.000	2(11.1%)	1(4.5%)	0.579

Note: PCOS = polycystic ovary syndrome, WD = Wilson disease

Table 6 Outcome of 40 patients WD comorbid with PCOS (Progesterone vs. Non-progesterone)

Outcome (PCOS)	Total (*n* = 40)	Progesterone (*n* = 13)	Non-progesterone (*n* = 27)	*P*
Menstruation restored	26(65%)	8(61.5%)	18(66.7%)	1.000
Pregnancy	5(12.5%)	1(7.7%)	4(14.8%)	1.000
Spontaneous abortion	3(7.5%)	0	3(11.1%)	0.538
Procreation	3(7.5%)	1(7.7%)	2(7.4%)	1.000

Note: PCOS = polycystic ovary syndrome, WD = Wilson disease

of these patients included hepatic/neuropsychiatric symptoms, abnormal menstruation, and hyperandrogenism. Testosterone level was significantly higher in the PCOS patients with non-WD than in the patients with WD. The incidence of clinical hyperandrogenism is significantly more prevalent in the adolescent subgroup of PCOS-WD. The hepatic fibrosis index showed positively correlation with the testosterone level. In followed-up observations, no significant difference was found in menstrual cycle and pregnancy outcomes between copper chelation therapy with progesterone and without progesterone. Our findings highlighted the distinct clinical, hormonal, and biochemical characteristics of WD patients with PCOS, and would contribute to the expanded understanding of endocrine comorbidity in WD. Additionally, we provided preliminary evidence suggesting a correlation between liver damage in WD and hormone levels associated with PCOS. This study lays the groundwork for further investigation into the causal relationship between these two conditions, and offers a clinical foundation for the long-term management on the patients of WD with comorbid PCOS.

Although WD mainly presented with hepatic or neuropsychiatric features [21, 22], various abnormalities of endocrine system, such as amenorrhea, infertility or repeated miscarriages, have been observed in patients with WD [23]. In our present study, irregular menstruation occurred in all the patients and clinical hyperandrogenism occurred in majority of the patients. Imaging tests showed no pituitary hyperplasia and intracranial space occupation, which excluded lactation, pregnancy, and pituitary tumor as the causes of amenorrhea. Previous studies have confirmed that high copper has adverse effects on the female endocrine system, especially ovarian function [24, 25]. Therefore, we speculate that the symptoms of endocrine abnormalities may associated with the toxicity of copper and liver damage in WD patients.

In our present study, 90% of the patients showed liver cirrhosis in ultrasound examination. As reported in the previous studies, increased testosterone concentration secondary to liver dysfunction leads to impaired ovarian function [26]. We found the clinical hyperandrogenism was also prevalent in PCOS-WD patients especially in adolescent subgroup, suggested that impaired liver function in early WD would affect the synthesis level of hormones. Besides, hypogonadism caused by chronic liver disease is one of the most common causes of gonadal dysfunction in patients with WD [27]. Our research identified correlations between various liver function indices and hormonal levels. Notably, testosterone levels exhibited a positive correlation with the HFi. Liver function indices serve as indicators of the extent of liver damage associated with copper deposition. Additionally, hormonal levels are sensitive markers in the progression of PCOS. For example, previous reports have shown that an interference of ovarian follicular aromatase activity, possibly due to copper intoxication, might be the cause of ovulatory disturbances in patients with WD [28]. Therefore, the degree of liver damage due to

excessive deposition of copper in female WD patients may be associated with the hormone level involving the PCOS. Currently, we have only made initial observations regarding the link between liver damage and PCOS, but the causal relationship remains unclear. Future research may explore the management of liver damage during the early treatment phases of female WD patients to assess whether this strategy can prevent or alleviate the symptoms associated with PCOS. Such investigations could pave the way for more comprehensive analyses aimed at improving long-term treatment and prevention strategies for the female WD demographic.

The interplay between systemic inflammation and metabolic dysfunction in PCOS has been well-documented. For instance, elevated serum calprotectin levels have been proposed as markers of inflammation and insulin resistance, highlighting their role in exacerbating hyperandrogenism [29]. Similarly, telomerase activity, an emerging biomarker of cellular stress and aging, has been shown to correlate with metabolic disturbances in PCOS patients, especially those without obesity [30]. In the context of Wilson disease, where copper toxicity induces both systemic inflammation and liver dysfunction, it is plausible that these pathways are further amplified, contributing to the unique endocrine profile observed in PCOS-WD patients. Future research could focus on these biomarkers to elucidate the shared metabolic and inflammatory mechanisms underlying these comorbidities.

As reported, after WD was diagnosed and zinc sulfate treatment was administered, the patient's clinical status improved considerably [31]. In followed-up observations, copper chelation therapy with or without progesterone has achieved good prognosis in menstrual cycle and pregnancy outcomes. No significant differences in menstrual cycle and pregnancy outcomes were observed between the treatment groups. This lack of variation may be attributed to the limited sample size, which may not adequately capture the differences between the two groups. Additionally, this finding highlights the unique characteristics of the WD cohort, as hepatic cirrhosis can be reversed through copper chelating therapy [32], and liver function is closely linked to various hormone levels involved in the abnormal menstrual cycle. Therefore, regular treatment with a copper chelating agent is crucial in WD patients with comorbid PCOS. Future research will involve increasing the sample size and conducting follow-up assessments to draw more definitive conclusions.

Several limitations are also included in the study. The sample size was constrained because WD is a rare condition, and its occurrence in conjunction with PCOS is even less common. And in clinical settings, the endocrine manifestations of WD are frequently overlooked, influenced by cultural or demographic factors specific to the Chinese cohort. Future research will focus more on endocrine symptoms in female patients with WD. Larger clinical cohort studies are necessary to yield more definitive evidence. Additionally, multi-center prospective studies of standard dosage regimens are required to validate the standardized treatment protocols moving forward. It is recommended to explore whether specific treatments (e.g. zinc, progesterone) have differential effects based on liver fibrosis severity or hormonal profiles as the future directions.

Conclusion

In conclusion, PCOS is also an important endocrine comorbidity of female WD patients. The study recommends routine screening for PCOS in adolescent WD patients. Testosterone levels may serve as a valuable reference for informing treatment decisions. Copper chelation therapy with or without progesterone is beneficial to the recovery of patients with PCOS-WD.

Acknowledgements
The authors thank the department of Neurology Institute in Anhui University of Chinese Medicine for the permission to conduct this study. In addition, the authors thank all the patients who participated in this study.

Author contributions
L.C. and Y.X. wrote the main manuscript text and L.C. prepared figures and all tables. All authors reviewed and revised the manuscript.

Funding
This study was funded by the Natural Science Foundation of Anhui Province (Grant number: 2308085QH290), Key Project of Natural Science Research Project of Universities in Anhui Province (Grant number: 2024AH050984), and High-level talent support plan of Anhui university of Chinese medicine (Grant number: DT2300000270).

Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethical approval and consent to participate
The study adhered to the tenets of the *Declaration of Helsinki*. This study was approved by Medical Ethics Committee of the Affiliated Hospital of the Neurology Institute in Anhui University of Chinese Medicine (Approval Number: 2023-SYSFYSY-31), and all patients gave written informed consent before participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Author details
[1]Institute of Neurology, Anhui University of Chinese Medicine, No. 357, Changjiang Middle Road, Hefei 230061, China

Received: 5 December 2024 / Accepted: 10 March 2025
Published online: 24 March 2025

References

1. Mulligan C, Bronstein JM. Wilson disease: an overview and approach to management. Neurol Clin. 2020;38:417–32.
2. European Association for Study of Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol. 2012;56:671–85.
3. Sandahl TD, Laursen TL, Munk DE, Vilstrup H, Weiss KH, Ott P. The prevalence of Wilson's disease: an update. Hepatology. 2020;71:722–32.
4. Poujois A, Woimant F. Challenges in the diagnosis of Wilson disease. Ann Transl Med. 2019;7(Suppl 2):S67.
5. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106:6–15.
6. McCartney CR, Marshall JC. Polycystic ovary syndrome. N Engl J Med. 2016;375:54–64.
7. McCartney CR, Marshall JC. Clinical Practice. Polycystic ovary syndrome. N Engl J Med. 2016;375:54–64.
8. Meier RK. Polycystic ovary syndrome. Nurs Clin North Am. 2018;53:407–20.
9. Kapoor N, Shetty S, Thomas N, Paul TV. Wilson's disease: an endocrine revelation. Indian J Endocrinol Metab. 2014;18:855–7.
10. Krysiak R, Handzlik-Orlik G, Okopien B. Endocrine symptoms as the initial manifestation of Wilson's disease. Yale J Biol Med. 2012;85:249–54.
11. Dzieżyc K, Litwin T, Członkowska A. Other organ involvement and clinical aspects of Wilson disease. Handb Clin Neurol. 2017;142:157–69.
12. Yu X-E, Pan M, Han Y-Z, Yang R-M, Wang J, Gao S. The study of Wilson disease in pregnancy management. BMC Pregnancy Childbirth. 2019;19:522.
13. Sinha S, Taly AB, Prashanth LK, Arunodaya GR, Swamy HS. Successful pregnancies and abortions in symptomatic and asymptomatic Wilson's disease. J Neurol Sci. 2004;217:37–40.
14. Tarnacka B, Rodo M, Cichy S, Członkowska A. Procreation ability in Wilson's disease. Acta Neurol Scand. 2000;101:395–8.
15. Mohr I, Pfeiffenberger J, Eker E, Merle U, Poujois A, Ala A, et al. Neurological worsening in Wilson disease - clinical classification and outcome. J Hepatol. 2023;79:321–8.
16. Alhermi A, Perks H, Nigi V, Altahoo N, Atkin SL, Butler AE. The role of the liver in the pathophysiology of PCOS: A literature review. Biomolecules. 2025;15:51.
17. Vassilatou E. Nonalcoholic fatty liver disease and polycystic ovary syndrome. World J Gastroenterol. 2014;20:8351–63.
18. Liu D, Gao X, Pan X-F, Zhou T, Zhu C, Li F, et al. The hepato-ovarian axis: genetic evidence for a causal association between non-alcoholic fatty liver disease and polycystic ovary syndrome. BMC Med. 2023;21:62.
19. Dzieżyc-Jaworska K, Litwin T, Członkowska A. Clinical manifestations of Wilson disease in organs other than the liver and brain. Ann Transl Med. 2019;7(Suppl 2):S62.
20. As P, Sf W, Km H, Se O, Mg V. M M, Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020;18.
21. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. Gut. 2007;56:115–20.
22. Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology. 2008;47:2089–111.
23. Erkan T, Aktuglu C, Gülcan EM, Kutlu T, Cullu F, Apak H, et al. Wilson disease manifested primarily as amenorrhea and accompanying thrombocytopenia. J Adolesc Health. 2002;31:378–80.
24. Chen Y, Guan F, Wang P, Liu W, Zhang W, Sun H, et al. Copper exposure induces ovarian granulosa cell apoptosis by activating the caspase-dependent apoptosis signaling pathway and corresponding changes in MicroRNA patterns. Ecotoxicol Environ Saf. 2023;264:115414.
25. Wang Q, Sun Y, Zhao A, Cai X, Yu A, Xu Q, et al. High dietary copper intake induces perturbations in the gut microbiota and affects host ovarian follicle development. Ecotoxicol Environ Saf. 2023;255:114810.
26. Kaushansky A, Frydman M, Kaufman H, Homburg R. Endocrine studies of the ovulatory disturbances in Wilson's disease (hepatolenticular degeneration). Fertil Steril. 1987;47:270–3.
27. Karagiannis A, Harsoulis F. Gonadal dysfunction in systemic diseases. Eur J Endocrinol. 2005;152:501–13.
28. Oga M, Matsui N, Anai T, Yoshimatsu J, Inoue I, Miyakawa I. Copper disposition of the fetus and placenta in a patient with untreated Wilson's disease. Am J Obstet Gynecol. 1993;169:196–8.
29. Hancerliogullari N, Tokmak A, Guney G, Pekcan MK, Koc EM, Candar T, et al. Serum calprotectin levels as markers of inflammation, insulin resistance and hyperandrogenism in women with polycystic ovary syndrome. Med (Baltim). 2022;101:e32326.
30. Unlu C, Guney G, Tugrul Ersak D, Kosem A, Tarlan N, Tokmak A. Evaluation of serum telomerase activity in normal-weight young girls with polycystic ovary syndrome and its relation to metabolic parameters. J Pediatr Endocrinol Metab. 2023;36:283–9.
31. Krysiak R, Okopień B. [Hyperprolactinaemia–like symptoms in Wilson's disease]. Pol Merkur Lekarski. 2008;25:61–3.
32. Das MC, Sen Sarma M, Srivastava A, Yachha SK, Poddar U. Effect of chelation therapy in pediatric Wilson's disease: liver and endoscopic outcome. J Hepatobiliary Pancreat Sci. 2021;28:336–45.

Publisher's note