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Clinical characteristics of patients under 40 years old with early-onset hyperuricaemia: a retrospective monocentric study in China

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ABSTRACT

Objective To investigate the clinical characteristics of patients with early-onset hyperuricaemia (HUC).

Methods A retrospective study using data from the Second Affiliated Hospital of Soochow University was conducted. 623 patients with HUC were divided into early-onset group and late-onset group. Another 201 healthy subjects ≤40 years old were regarded as control group. The data of physical measurements and biochemistry test were collected. Clinical data of early-onset group were compared with late-onset group and control group by analysis of variance (ANOVA) and χ^2 test. Principal component analysis (PCA) was applied. Logistic regression was used to identify the clinical factors correlated with patients with early-onset HUC.

Results The patients of early-onset group had different body mass index (BMI), serum albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma-glutamyltransferase (GGT), creatinine (Cr), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), TG/high density lipoprotein (HDL) ratio, HDL and percentage of males, hypertension (HBP) as well as fatty liver compared with healthy people in the control group. Early-onset group patients had different albumin, ALT, fasting blood glucose, Cr, percentage of males and HBP compared with late-onset group patients. PCA identified four significant patterns including PC1 (labelled 'TG and HDL'), PC2 (labelled 'fatty liver and liver enzymes'), PC3 (labelled 'TC and LDL') and PC4 (labelled 'AKP'). The results of univariate and multivariate logistic regression analysis showed that BMI, HBP and albumin were correlative factors for early onset of HUC when the patients with early-onset and late-onset HUC were involved, while gender, BMI, PC1, PC2 and PC4 were correlative factors for early-onset HUC when the early-onset and control groups were involved.

Conclusion This study described a group of patients with early-onset HUC with distinct clinical features. Gender, BMI, 'TG and HDL', 'fatty liver and liver enzymes' and 'AKP' have higher values than HBP, type 2 diabetes mellitus and 'TC and LDL' in patients under 40 years old with early-onset HUC.

Strengths and limitations of this study

- This study focused on patients under 40 years old with the early-onset hyperuricaemia (HUC) .
- The result of this study showed several factors correlated with patients with early-onset HUC.
- This is a retrospective research and the causality cannot be revealed.
- The single-centre setting may limit the generalisability of the results.
- Several important data like the drinking history are not contained in this research.

BACKGROUND

Hyperuricaemia (HUC) is one of the most common manifestations of metabolic disorders. It is related to many factors such as age, sex, genetics, lifestyle and environment, and it is associated with many diseases, including gout, diabetes mellitus, hypertension (HBP), stroke, dyslipidaemia, chronic kidney disease, cardiovascular events and heart failure.[1–4] Especially, HUC is the main cause of gout, which contributes a growing burden of disease worldwide.[5 6] According to an Australian review, the prevalence of HUC and gout increased during a 30-year period from 0.5% to 1.7%.[7] In China, the prevalence of gout and HUC was 13.3% and 1.1%, respectively.[8] Although gout mostly occurs after middle age, the number of patients experiencing its onset at a younger age is now increasing.[9–12] The clinical characteristics of early-onset gout were reported to be distinct from those of late-onset gout.[13]

Patients of late-onset HUC usually have three or more kinds of metabolic disorders, which may interact with each other and make it difficult to clarify the most important mechanism of HUC.[14 15] Young people are different from the old, they have different lifestyles and hormone levels and the morbidity of complications are lower.[16] Some researches tried to describe the pathogenesis and clinical features about early-onset gout and HUC.[13 17–19] Yan and her colleagues observed that elevated levels of total cholesterol (TC),

triglyceride (TG) and low density lipoprotein (LDL) were independent risk factors for HUC.[20] TC and TG associated with HUC are more frequent in the young people (30–39 years) than in the old-aged ones (≥60 years).[21] Chen *et al* observed that hypertriglyceridaemia, not hypercholesterolemia, in young patients with HUC was significantly higher than that in the old-age groups.[14] However, studies on early-onset HUC and gout are still lacking.

Studying patients with early-onset HUC can help us to have a better understanding of the early stage of HUC, thus to provide a new way to prevent or treat HUC. For this purpose, we conducted a retrospective research to analyse the clinical characteristics of patients with early-onset HUC.

METHODS

Subjects

A single-centre, retrospective study was conducted at the Second Affiliated Hospital of Soochow University from April 2013 to July 2017. Six hundred and twenty-three subjects with HUC or gout who came to the hospital were enrolled in this study. Based on the age of onset, they were divided into the early-onset HUC group (n=287, ≤40 years old) and the late-onset HUC group (n=336, >40 years old).[11] In addition, 201 healthy subjects under 40 years old without HUC from the physical examination centre or from outpatient department for physical examination were also included in the control group. Those HUC people who were undergoing urate-lowering therapy or chronic steroid therapy were excluded. Besides, we also searched for the previous history of the patients with HUC and excluded those who could not remember the precise age of onset with HUC.

The HUC was defined as ≥420 µmol/L for men and ≥360 µmol/L for women.[18] HBP was defined as systolic pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the current use of antihypertensive medication.[22]

Variables

Clinical characteristics, namely gender, age, comorbid diseases including HBP and type 2 diabetes mellitus (T2DM), body height, blood pressure and body mass index (BMI) were recorded. Serum biochemistry results were also obtained, including creatinine (Cr), alanine transaminase (ALT), aspartate aminotransferase(AST), alkaline phosphatase (AKP), gamma-glutamyltransferase (GGT), albumin, serum uric acid (SUA), fasting blood glucose (FBG), lipid profiles such as TC, high density lipoprotein (HDL), LDL and TG. TG:HDL ratio was calculated as TG divided by HDL. Results of the abdominal B-ultrasonography examinations were also collected to seek whether the subjects had fatty liver or not.

Statistical analysis

Data were summarised as mean±standard deviation (continuous variables) or percentage (categorical variables). The continuous variables among three groups were compared by one-way analysis of variance (ANOVA), categorical variables were compared by χ^2 test. All continuous variables were plotted into a quantile–quantile plot for normality check. Principal component analysis (PCA) based on LDL, TG, TC, HDL, TG:HDL ratio, ALT, AST, GGT, AKP and fatty liver was applied as a dimension reduction method and to avoid the multicollinearity. The continuous variables were standardised based on z-score before PCA. The number of principal components (PCs) was determined based on the Scree plot. Factor loadings were considered significant for coefficients ≥0.3. Promax rotation was used to facilitate easy interpretation of components. Four PC scores were generated (PC1 score, PC2 score, PC3 score and PC4 score) for each patient. Univariate and multiple logistic regressions were applied and variables were selected by stepwise regression. The logistic regression model contained variables including age, gender, BMI, albumin, HBP, T2DM and 4PCs. The Pearson χ^2 test[23] was evaluated to check the overall model fit. P value <0.05 was defined as significant.

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross sectional checklist when writing our report.[24]

Patient and public involvement

This study was a retrospective study based on abstraction of medical records. The study does not include patient advisors, as patients were not involved in the recruitment or conduct of the study. The study findings will not be disseminated directly to patients, although the findings will inform quality improvement initiatives in hospitals after the dissemination of the study results.

RESULTS

Baseline characteristics

Eight hundred and twenty-four participants were enrolled in the study, including 287 (34.8%) in the early-onset group, 336 (40.8%) in the late-onset group and 201 (24.4%) healthy people in the control group. Five hundred and sixty-nine of the patients with HUC were asymptomatic. Among them, there were only 52 (6.3%) female patients with HUC in the study, and 16 in the early-onset group and 36 in the late-onset group. In the control group, the number of women was 102. These are summarised in table 1.

Distinct clinical features of patients in three groups

The results of multiple comparisons are listed in table 1. When compared with the patients with late-onset HUC, the patients with early-onset HUC had higher serum ALT and higher percentage of fatty liver, while serum Cr, FBG and the percentage of HBPs and diabetes were lower (p value<0.05). When compared with the control group, the patients of early-onset group had higher BMI, Cr, ALT, AST, GGT, albumin, uric acid (UA), TC, LDL, TG, TG/HDL ratio, percentage of fatty liver and HBPs and lower

Table 1 Clinical characteristics of the subjects in the study divided by early-onset, late-onset and control groups

	Early-onset group (n=287)	Late-onset group (n=336)	Control group (n=201)
Age (years)	31.9±5.06	59.54±12.18*	32.49±4.43
Gender (male)	271 (94.4%)	300 (89.3%)	99 (49.3%)*
BMI	26.09±3.25	25.43±3.79	22.10±3.16*
Fatty liver (yes)	158 (55.1%)	137 (40.8%)*	28 (13.9%)*
HBP (yes)	56 (19.5%)	103 (30.7%)*	12 (6%)*
Diabetes (yes)	8 (2.8%)	23 (6.8%)*	1 (0.5%)
SUA (mg/dL)	475.98±76.54	458.72±102.36	302.62±68.31*
Cr (μmol/L)	77.48±11.00	83.67±28.64*	65.13±14.07*
Albumin (g/L)	49.10±2.33	47.09±2.55*	48.16±2.44*
FBG (mmol/L)	5.04±2.27	5.44±1.16*	4.81±0.47
TC (mmol/L)	5.35±0.85	5.40±0.97	4.91±0.80*
TG (mmol/L)	2.04±1.32	2.11±1.65	1.10±0.65*
HDL (mmol/L)	1.20±0.76	1.23±0.36	1.47±0.35*
LDL (mmol/L)	3.44±0.79	3.37±0.88	2.91±0.80*
TG:HDL ratio	2.03±1.82	2.02±2.23	0.88±0.81*
AKP (IU/L)	74.08±18.09	72.44±16.51	59.17±16.21*
ALT (U/L)	40.87±38.54	29.67±24.47*	19.10±15.13*
AST (U/L)	24.64±12.01	23.91±12.03	17.62±0.43*
GGT	51.33±57.19	44.91±44.74	21.91±17.90*

Statistics are reported as mean±standard deviation (continuous variable) or number and percentage (categorical variables).
*P<0.05 (compared with early-onset group by one-way ANOVA or χ^2 test).
AKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase;BMI, body mass index; Cr, creatinine; FBG, fasting blood-glucose; GGT, gamma-glutamyltransferase; HBP, high blood pressur; HDL, high density lipoprotein; LDL, low density lipoprotein; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride.

HDL (p value<0.05). However, there was no difference in the percentage of T2DM.

Correlative factors for early-onset HUC

PCA identified four significant patterns, accounting for 76.9% of the overall variance. PC1=24.3%, PC2=23.8%, PC3=19.7% and PC4=10.1%. PC1 included fatty liver, TG, HDL and TG/HDL ratio, labelled 'TG and HDL'. PC2 included fatty liver, ALT, AST and GGT, labelled 'fatty liver and liver enzymes'. PC3 included LDL and TC, labelled 'TC and LDL', PC4 included AKP, labelled 'AKP' (table 2).

Univariate logistic regression analysis including age, gender, HBP, T2DM, BMI, albumin and 4PCs was applied, followed by multiple logistic regression. Table 3 presents the OR and corresponding CI for early-onset HUC when early-onset and late-onset groups were contained in the analysis. After adjusting the effects of potential confounders except for age, there was no significant association between T2DM and 4PCs. HBP was negatively associated with early-onset HUC (OR 0.212; 95% CI=0.132 to 0.339 ; p value<0.001). On the other hand, BMI (OR 1.098; 95% CI=1.028 to 1.172; p value=0.005) and albumin (OR 1.371; 95% CI=1.249 to 1.504; p value<0.001) were positively associated with early-onset HUC. Table 4 presents the OR and corresponding CI for early-onset HUC when early-onset and control groups were contained in the analysis. Gender (male) (OR 17.237; 95% CI=6.669 to 44.553; p value<0.001), BMI (OR 1.281; 95% CI=1.151 to 1.427; p value<0.001), PC1 (OR 1.473; 95% CI=1.001 to

Table 2 Rotated component matrix

	Components			
Variables	1	2	3	4
Fatty liver (yes)	0.374	0.371		
ALT (U/L)		0.918		
AST (U/L)		0.896		
AKP (U/L)				0.963
GGT (U/L)		0.683		
TC (mmol/L)			0.957	
TG (mmol/L)	0.911			
HDL (mmol/L)	–0.693			
LDL (mmol/L)			0.946	
TG/HDL ratio	0.946			

AKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; LDL, low density lipoprotein;TC, total cholesterol; TG, triglyceride.

Table 3 Results of univariate and multiple logistic regression analysis involving early-onset and late-onset groups

Variable	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender (male)	3.707 (1.754 to 7.835)	0.001	–	–
T2DM	0.430 (0.188 to 0.986)	0.046	–	–
HBP (yes)	0.327 (0.221 to 0.484)	<0.001	0.212 (0.132 to 0.339)	<0.001
BMI	1.057 (1.001 to 1.116)	0.044	1.098 (1.028 to 1.172)	0.005
Albumin (mmol/L)	1.413 (1.306 to 1.528)	<0.001	1.371 (1.249 to 1.504)	<0.001
PC1	1.006 (0.865 to 1.170)	0.941	–	–
PC2	1.221 (1.041 to 1.431)	0.014	–	–
PC3	0.955 (0.817 to 1.116)	0.562	–	–
PC4	1.113 (0.945 to 1.310)	0.201	–	–

Gender, BMI, albumin, HBP, T2DM and 3PCs were contained in the stepwise logistic regression.
The fit was checked by Pearson χ^2 test.
PC1 includes fatty liver, TG, HDL and TG/HDL ratio; PC2 includes fatty liver, ALT, AST, AKP and GGT; PC3 includes LDL and TC.
BMI, body mass index;HBP, hypertension.

2.171; p value=0.048), PC2 (OR 1.757; 95% CI=1.108 to 2.786; p value=0.016) and PC4 (OR 1.801; 95% CI=1.324 to 2.449) were all positively associated with early-onset HUC.

DISCUSSION

Our study demonstrated that gender had significant effect (OR 17.237) on HUC in people under 40 years old and the same results had also been reported by other researchers.[25] Different hormone levels and lifestyles may be related to the big difference of UA metabolism between men and women.[26]

According to the previous researches, HUC was associated with many metabolic disorders including hypertriglyceridemia, HBP, hypercholesterolemia, obesity and diabetes.[27 28] In consideration of close relationship between HUC and metabolic syndrome, most variables involved in this study were associated with metabolic syndrome. The results of this study also showed that most clinical characteristics associated with metabolic syndrome also associated with HUC.

BMI was one of the variables most significantly associated with the occurrence of metabolic syndrome in HUC[29–31] and the percentage of overweight in patients with HUC was increasing.[10] Our results also find that patients with early-onset HUC also had a significantly higher BMI (OR 1.281) compared with the healthy people of the same age, which was in accordance with the previous researches.[13 19] Obesity could result in an insulin resistant state and compensatory increase in insulin secretion.[32] Hyperinsulinemia may result in hyperlipidemia and HUC, and decrease the renal clearance of UA as well.[33] The fact that patients with early-onset HUC had higher BMI in this study helped to

Table 4 Results of univariate and multiple logistic regression analysis involving early-onset and control groups

Variable	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	0.975 (0.938 to 1.012)	0.184	–	–
Gender (male)	36.597 (17.823 to 75.146)	<0.001	17.237 (6.669 to 44.553)	<0.001
T2DM	2.853 (0.599 to 13.579)	0.188	–	–
HBP (yes)	4.062 (2.113 to 7.807)	<0.001	–	–
BMI	1.493 (1.375 to 1.620)	<0.001	1.281 (1.151 to 1.427)	<0.001
Albumin (mmol/L)	1.182 (1.091 to 1.280)	<0.001	–	–
PC1	4.720 (3.272 to 6.810)	<0.001	1.473 (1.001 to 2.171)	0.048
PC2	4.079 (2.717 to 6.123)	<0.001	1.757 (1.108 to 2.786)	0.016
PC3	1.691 (1.362 to 2.099)	<0.001	–	–
PC4	2.014 (1.610 to 2.519)	<0.001	1.801 (1.324 to 2.449)	<0.001

Age, gender, BMI, albumin, HBP, T2DM and 3PCs were contained in the stepwise logistic regression.
The fit was checked by Pearson χ^2 test.
PC1 includes fatty liver, TG, HDL and TG/HDL ratio; PC2 includes fatty liver, ALT, AST, AKP and GGT; PC3 includes LDL and TC.
BMI, body mass index; HBP, hypertension.

prove that insulin resistant exists in young patients with HUC. In future studies, we will further demonstrate this hypothesis.

In this study, we also found positive association between early-onset HUC and PC1, which mainly included HDL, TG, TG/HDL ratio and fatty liver in people under 40 years old. According to the result of multiple logistic regression, the relationship of early-onset HUC and PC1 was independent of age, gender and BMI. HDL seemed to have another way to connect with the early onset of HUC independent of obesity. Recent study showed that HUC was associated with the increase of insulin release in healthy non-obese subjects with normal glucose tolerance.[34] The relation of the changes in HDL with insulin resistance is partly independent of obesity, arising in concert with the changes in TG-rich lipoprotein metabolism.[35 36] Some research reports that TG:HDL ratio, an insulin resistance marker, may be a useful tool to identify high-risk individuals of HUC.[37] Fatty liver, the fourth component of PC1, was also proved to be mediated by insulin resistance.[38] However, more researches are needed to figure out whether PC1 is connected with insulin resistance and how it correlate with early-onset HUC.

Logistic regression showed that PC2 (OR 1.757) and PC4 (OR 1.801) were risk factors of early-onset HUC. Fatty liver, which is included in both PC1 and PC2, is significantly associated with early-onset HUC.[39 40] The other components of PC2 and PC4 including ALT, AST, GGT and AKP may stand for the liver injury. This study showed the positive correlation between HUC under 40 years old and liver damage such as fatty liver. It has been reported that the association between fatty liver and HUC can also be independent of insulin resistance and other metabolic disorders.[41] Previous studies have shown that index of liver damage, such as elevated ALT is combined with genetic susceptibility to inflammation associated with increased SUA levels.[42] A further study showed that SUA is independently associated with elevated ALT.[43] UA can also aggravate the oxidative stress response in hepatocytes and adipocytes.[44]

PC3 mainly included LDL and TC, and our results showed no significant correlation with early-onset HUC. The association between HUC and LDL/TC is not completely clear. It is reported that serum LDL cholesterol and TC are strongly associated with SUA levels.[45] However, in their study, HUC in young patients was not analysed separately. In this study, LDL and TC were higher in the early-onset group than those in the control group. However, when adjusted by BMI, the result of multiple logistic regression showed that PC3 is not the independent correlative factor. It is reported that oxidised LDL, not total LDL concentrations is associated with metabolic syndrome independently of central obesity and insulin resistance.[46] It is a pity that oxidised LDL was not tested in this study. We will observe whether oxidised LDL is associated with early-onset HUC in people under 40 years old in our future work.

HUC was proved to be associated with an increased risk of HBP.[47] As to a report, a total of 69.5% of patients with gout had HBP and 17.9% had diabetes in Korean.[48] A 10-year cohort study also showed that the increasing quartiles of SUA were associated with 10-year incidence of HBP.[49] However, there was no significant difference of the incidence of HBP between the early-onset group and control group. HBP in patients with early-onset HUC may be associated with insulin resistance. Elevated fasting insulin concentrations or insulin resistance was independently associated with an exacerbated risk of HBP,[50] and short-term aerobic exercise training improves insulin sensitivity.[51] In our study the correlation between HBP and HUC was invisible in people under 40 years old, which was consistent with previous studies.[15] May be the young patients with HUC were in a prehypertension stage.

T2DM was another member of metabolic syndrome and is proved to be related with HUC.[52] However, in this study, T2DM is not a significant association with early-onset HUC. People with insulin resistance may develop to pre-diabetes and then to T2DM, but it takes several years.[53] Krishnan *et al* conducted a 15-year follow-up study and found that HUC was an independent marker for predicting diabetes and pre-diabetes among young adults in the subsequent 15 years.[54] In their study, the average value of baseline plasma glucose level was normal, regardless of the serum urate level. The subjects with early-onset HUC in this study were under 40 years, they may be just in insulin resistance or pre-diabetes stage.[53] We will test the insulin level in the next study. Besides, longer time observation may lead to a consistent conclusion.

There were still several limits in our study. First, it was a retrospective monocentric research and the sample size was limited. Second, some important data like the history of alcohol intake and the family history of HUC or gout were not acquired. Third, not all patients were diagnosed using liver ultrasonography and they were removed from this research, this could lead to a bias of the sample. Fourth, there were nearly 20 variables in this study and the results of multiple comparisons were not adjusted, the applicability of the multiple comparisons result was limited. Finally, there was an obvious difference of the average age between early-onset and late-onset groups. Since these two groups were divided based on age, age was not adjusted in the multiple logistic regression. Although the results of multiple logistic regression showed HBP, BMI and albumin as correlative factors of early-onset HUC, the confounding factors brought by age could not be ignored. A well-designed prospective study, would be helpful for further studies of patients with early-onset HUC.

In conclusion, this study described a group of patients with early-onset HUC with distinct clinical features. We found several factors which have significant correlations with early-onset. Gender, BMI, 'TG and HDL', 'fatty liver and liver enzymes' and 'AKP' showed significant correlation with early-onset HUC in people under 40 years old, but not HBP, T2DM and 'TC and LDL'. More researches

are needed to reveal the clinical characteristics and the possible pathogenesis of early-onset HUC, thus to find a new way to prevent or treat this disease.

Contributors ZL designed the study and revised drafts of the paper . YZ was responsible for statistical analysis and wrote the paper. YY provided most of the laboratory data. LX, JW, LB, MT, RY and DY were responsible for the collection of the data of the outpatients. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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