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Research article

Intrahepatic cholestasis of pregnancy worsening perinatal depressive tendency: A follow-up study from the second trimester to the sixth week postpartum

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ABSTRACT

The total bile acid (TBA) is usually used to diagnose intrahepatic cholestasis of pregnancy (ICP) as a common clinical index. Recently many research reports on the microbiota-gut-brain axis (MGB axis) suggest that bile acids have an influence on human mental illnesses such as anxiety and depression, linked closely to intestinal microbial population. However, there is still a lack of clinical data to support intrinsic relationships about human cases. In this study, we conducted a follow-up study of 25 ICP and 98 healthy pregnant women to investigate the influence of ICP disease on perinatal depression. To further explore the effect of TBA concentration, we reviewed data of another 41 ICP women then added their cross-sectional data. The results showed that ICP disease increased mental scale scores but a conventional efficient treatment by using ursodeoxycholic acid (UDCA) could not decrease scores, suggesting intrahepatic cholestasis might make some key bile acids not to be processed by gut microbiota. UDCA could not replace the function of gut microbiota for easing depression and the change of bile acid composition in intestines worsened perinatal depressive tendency through the MGB axis.

1. Introduction

Bile acids are major components of bile, playing an important role in cholesterol, lipid, glucose, and energy metabolism in liver, intestine and other organs [1,2]. The liver in human body is the only organ with all the enzymes required for bile acid synthesis, such as the rate-limiting enzyme cholesterol 7a-hydroxylase (CYP7A1, initiating the classic bile acid synthesis pathway), mitochondrial sterol 27-hydroxylase (CYP27A1, initiating the alternative bile acid synthesis pathway) and other subsequent enzymes. The primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are conjugated with taurine or glycine, from liver across the canalicular membrane to enter the bile. Then gut microbiota make the primary bile acids modified (mainly deconjugation and 7α-dehydroxylation) to form the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) [3]. Bile acids are reabsorbed in the terminal ileum, then transported through the portal vein back to the liver. Modifying specific bile acids by gut microbiota links liver and brain, through the enterohepatic circulation and the microbiota-gut-brain axis (MGB axis). The MGB axis is a complex

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bidirectional communication channel between the gut and the brain, through regulating the function of hypothalamic-pituitary-adrenal axis (HPA axis), the inflammatory response induced by the immune system and the regulation of neuroendocrine metabolites to affect depression [4].

In addition, bile acids enter the circulatory system and cross the blood-brain barrier, working on the brain. Generally, bile acids are endogenous ligands activating a complex network of nuclear receptor farnesoid X receptor (FXR) and membrane G protein-coupled bile acid receptor-1 (Gpbar-1) [2]. They are effective signaling pathways, inhibiting NF-kB-induced inflammatory cytokine production and liver inflammation and protecting against inflammation in the liver and intestine. Besides the most well-studied receptors FXR and Gpbar-1, there are other bile acid-regulated receptors such as NMDAR (N-methyl-D-aspartate receptor), $GABA_AR$ (gamma-aminobutyric acid receptor), S1PR2 (shingosine-1-phospate receptor 2), M3 (muscarinic acetylcholine receptor M3), PXR (pregnane X receptor), VDR (vitamin D receptor), GR (glucocorticoid receptors) and so on, associated to the critical neuroactive regulators to brain activity and function [5].

The ICP disease is an unknown pathological condition during the second and third trimesters (pregnancy complication), with inevitable raised TBA, contingent pruritus and rare jaundice. Geographical location and ethnicity have a great influence on the ICP incidence, which rate in China is <1% [6]. The change of bile acid composition may be related to gut microbiota metabolism [7] and has an impact on mental state [8]. The perinatal period is also an important transition, which results to developing mental health disorders such as perinatal depression (incidence rate at about 20% among Asian pregnant women) [9]. Poor social relationships and stress is generally considered to be a major factor leading to perinatal depression, but a gene-environment interaction could not be ignored either [9,10]. The ICP women are inevitably complicated with this change, so it is meaningful to research the relationship between the ICP disease and the perinatal depression.

In this study, we conducted a follow-up study of 25 ICP and 98 healthy pregnant women to investigate the influence of ICP disease on perinatal depression. Then we reviewed data of another 41 ICP women and added cross-sectional data to further explore the change of mental scale scores, in condition for decreasing TBA concentration by using UDCA (Fig. 1). We found some interesting statistical results: (1) The ICP disease increased mental scale scores (including Edinburgh during pregnancy depression scale and Edinburgh postnatal depression scale); (2) UDCA could not decrease the scores of ICP women, whose TBA had been fallen to normal level in serum (TBA<10 μmol/L) after a previous rise in this effective drug treatment.

2. Materials and methods

2.1. Study design, participant criteria and data collection

From January 2020 to December 2021, 164 pregnant women were enrolled in the study and their clinical data were collected from the medical records in Shaoxing Maternity and Child Health Care Hospital (Shaoxing, Zhejiang Province, China). Their mental scale data were collected from the Perinatal and Postpartum Depression Information Collection System, which had been created in previous studies [11]. At 28th week during their pregnancy, the pregnant women were tested for relevant biochemical indexes in serum and assessed for Edinburgh during pregnancy depression scale. At 6th week after their childbirth, participants who could be followed up were assessed for Edinburgh postnatal depression scale. Some of them were not followed up because they went to another hospital for treatment. In practice, the contents of fore-and-aft scales were same, and setting distinguished names were just to judge the time point

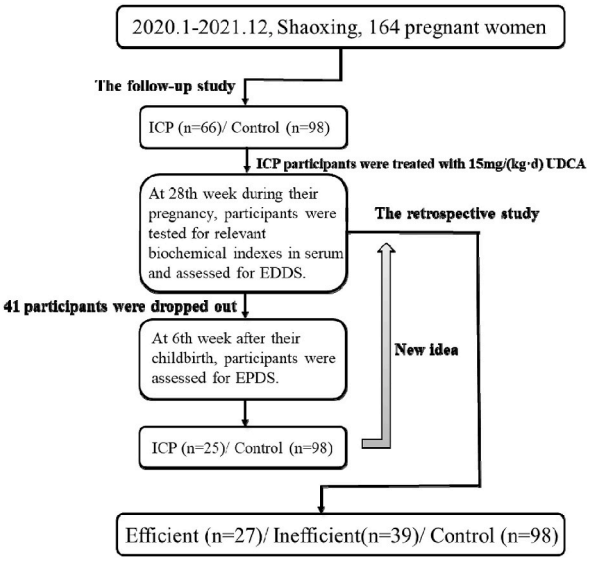

Fig. 1. The flow chart of the various ICP study. UDCA means ursodeoxycholic acid; EDDS means Edinburgh during pregnancy depression scale; EPDS means Edinburgh postnatal depression scale.

when women were assessed for mental scales. They were completed a study questionnaire with a trained research assistant. The study protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Shaoxing Maternity and Child Health Care Hospital (No. 2018050). All study participants were adults and written informed consent was obtained from them.

In this study, participants met the following inclusion criteria: married women were aged 20–40 years without any disease history of mental health problems (include generalized anxiety disorder, panic, agoraphobia, posttraumatic stress disorder, social phobia, depression disorder and so on), any severe systemic diseases (include heart, brain, liver, kidney, hematopoietic system and so on), or any history of drug abuse. ICP group consisted of pregnant women who were diagnosed with ICP disease in their early pregnant stage. They were also tested for virological test (including hepatitis virus, Epstein-Barr virus and cytomegalovirus) and examined for organic morphological exam by liver ultrasound technology. After being diagnosed as ICP disease, pregnant women in the ICP group were treated with 15mg/(kg·d) UDCA. Based on the result of their tested TBA index in serum at 28th week during pregnancy, women in the ICP group were divided into the effective or ineffective groups. Control group consisted of healthy pregnant women without any pregnancy complications (threatened abortion, gestational diabetes mellitus, hypertensive disorder, placenta previa, intrahepatic cholestasis of pregnancy, oligohydramnios, intrauterine growth restriction and so on).

2.2. Statistical analysis

All analyses in the study were conducted with SPSS20.0 (IBM, USA). For measurement data, Shapiro-Wilk Test was used to observe characteristics of normal distribution within each group. Levene's Test was used to judge homoscedasticity, when continuous variables were compared between two groups. Mann-Whitney *U* test was performed for comparisons between group, in cases of two groups of continuous variables. And the Bonferroni correction was used to counteract the error of multiple comparisons. For enumeration data, Person Chi-square Test and Fisher's exact Test were for Chi-square analysis. All reported probability values were 2-tailed, and P value < 0.05 indicates significance for statistical analysis.

Table 1
The statistical result from the follow-up study of ICP and control groups.

	ICP group		Control group		ICP group vs. Control group	
	n = 25	Shapiro-Wilk Test	n = 98	Shapiro-Wilk Test	Levene's Test	Mann-Whitney *U* Test
		P value		P value	P value	P value
Age (year), Mean ± SD	27.16 ± 2.69	0.562	28.02 ± 3.07	<0.001	0.61	0.311
BMI (kg/m^2), Mean ± SD	20.15 ± 3.96	<0.001	20.40 ± 2.89	<0.001	0.999	0.430
Higher education, Y/N	18/7		76/22			0.559^p
Parity, P/M	19/6		75/23			0.956^p
Current smoker, Y/N	0/25		3/95			1.000^f
Current alcohol consumption, Y/N	12/13		32/66			0.153^p
ART, Y/N	3/22		3/95			0.098^f
TBA (μmol/L), Mean ± SD	25.15 ± 21.17	0.005	3.41 ± 2.49	<0.001	<0.001	<0.001
ALT (IU/L), Mean ± SD	75.94 ± 107.93	<0.001	10.08 ± 4.51	<0.001	<0.001	<0.001
AST (IU/L), Mean ± SD	57.76 ± 65.33	<0.001	19.01 ± 6.05	<0.001	<0.001	<0.001
GGT (IU/L), Mean ± SD	34.74 ± 35.00	<0.001	15.05 ± 7.09	<0.001	<0.001	<0.001
ALP (IU/L), Mean ± SD	279.44 ± 99.31	0.273	201.14 ± 67.38	<0.001	0.002	<0.001
TC (mmol/L), Mean ± SD	6.53 ± 1.57	0.559	6.60 ± 1.33	<0.001	0.557	0.863
LDL (mmol/L), Mean ± SD	3.61 ± 1.41	<0.001	3.31 ± 0.96	<0.001	0.084	0.599
HDL (mmol/L), Mean ± SD	1.71 ± 0.41	0.228	1.93 ± 0.46	<0.001	0.414	0.048
HGB (g/L), Mean ± SD	122.48 ± 11.75	0.007	119.96 ± 15.18	<0.001	0.800	0.250
TB (μmol/L), Mean ± SD	12.77 ± 9.98	<0.001	8.98 ± 2.78	<0.001	<0.001	0.054
IB (μmol/L), Mean ± SD	9.27 ± 3.66	<0.001	7.74 ± 2.46	<0.001	0.33	0.015
DB (μmol/L), Mean ± SD	4.26 ± 6.90	<0.001	1.32 ± 1.01	<0.001	<0.001	<0.001
EDDS, Mean ± SD	7.28 ± 5.40	0.195	3.63 ± 3.01	<0.001	<0.001	0.001
EDDS≥10 (%), Percentage	32.00		5.10			0.001^f
EPDS, Mean ± SD	6.28 ± 6.02	0.014	2.85 ± 3.02	<0.001	<0.001	0.019
EPDS≥10 (%), Percentage	28.00		4.08			0.001^f
CES, Mean ± SD	1.00 ± 4.39	0.030	0.79 ± 3.63	0.001	0.205	0.952

The P value from Chi-square analysis to compare EDDS≥10 and EPDS≥10 percentages in control group is 1.000^f. The P value from Chi-square analysis to compare EDDS≥10 and EPDS≥10 percentages in ICP group is 0.758^p.

Word p in the upper right corner of numbers refers to result from Person Chi-square Test and word f similarly refers to Fisher's exact Test. P value < 0.05 indicates significance for statistical analysis.

Abbreviations in the table: SD means standard deviation; BMI means body mass index; Y/N means yes or no; P/M means primiparous or multiparous; ART means assisted reproductive technology; TBA means total bile acid; ALT means alamine aminotransferase; AST means aspartate aminotransferase; GGT means γ-glutamyltransferase; ALP means alkaline phosphatase; TC means total cholesterol; LDL means low density lipoprotein; HDL means high density lipoprotein; HGB means hemoglobin; TB means total bilirubin; IB means indirect bilirubin; DB means direct bilirubin; EDDS means Edinburgh during pregnancy depression scale; EPDS means Edinburgh postnatal depression scale; CES means change scale of EDDS to EPDS; Vs. means versus.

Table 2
The statistical result from the retrospective data of various ICP and control groups.

	Control group		Efficient group		Efficient group vs. Control group		Inefficient group		Inefficient group vs. Control group	
		Shapiro-Wilk Test	TBA<10 μmol/L	Shapiro-Wilk Test	Levene's Test	Mann-Whitney *U* Test	TBA≥10 μmol/L	Shapiro-Wilk Test	Levene's Test	Mann-Whitney *U* Test
	n = 98	P value	n = 27	P value	P value	P value	n = 39	P value	P value	P value
Age (year), Mean ± SD	28.02 ± 3.07	<0.001	28.07 ± 3.01	0.675	0.640	0.859	28.36 ± 4.53	0.001	0.043	0.967
BMI (kg/m^2), Mean ± SD	20.40 ± 2.89	<0.001	20.86 ± 4.44	<0.001	0.050	0.773	20.19 ± 2.68	0.183	0.868	0.881
Higher education, Y/N	76/22		21/6			0.980^p	26/13			0.187^p
Parity, P/M	75/23		22/5			0.585^p	27/12			0.377^p
Current smoker, Y/N	3/95		0/27			1.000^f	0/39			0.558^f
Current alcohol consumption, Y/N	32/66		7/20			0.504^p	18/21			0.139^p
ART, Y/N	3/95		5/22			0.012^f	5/34			0.042^f
TBA (μmol/L), Mean ± SD	3.41 ± 2.49	<0.001	6.13 ± 2.12	0.143	0.924	<0.001	38.07 ± 22.60	<0.001	<0.001	<0.001
ALT (IU/L), Mean ± SD	10.08 ± 4.51	<0.001	50.84 ± 52.41	<0.001	<0.001	<0.001	58.09 ± 89.28	<0.001	<0.001	<0.001
AST (IU/L), Mean ± SD	19.01 ± 6.05	<0.001	59.11 ± 51.69	<0.001	<0.001	<0.001	45.44 ± 49.25	<0.001	<0.001	<0.001
GGT (IU/L), Mean ± SD	15.05 ± 7.09	<0.001	46.82 ± 54.97	<0.001	<0.001	<0.001	27.99 ± 27.64	<0.001	<0.001	0.238
ALP (IU/L), Mean ± SD	201.14 ± 67.38	<0.001	255.59 ± 101.04	0.042	0.002	0.018	250.13 ± 110.96	0.094	<0.001	0.025
TC (mmol/L), Mean ± SD	6.60 ± 1.33	<0.001	6.54 ± 1.56	0.595	0.205	0.922	6.86 ± 1.83	0.002	0.215	0.602
LDL (mmol/L), Mean ± SD	3.31 ± 0.96	<0.001	3.76 ± 1.53	0.003	0.003	0.104	3.76 ± 1.30	0.004	0.067	0.045
HDL (mmol/L), Mean ± SD	1.93 ± 0.46	<0.001	1.55 ± 0.51	0.042	0.141	0.002	1.74 ± 0.40	0.210	0.350	0.001
HGB (g/L), Mean ± SD	119.96 ± 15.18	<0.001	115.12 ± 16.72	0.207	0.106	0.196	117.74 ± 14.86	0.011	0.227	0.572
TB (μmol/L), Mean ± SD	8.98 ± 2.78	<0.001	10.35 ± 4.27	<0.001	0.031	0.171	12.31 ± 9.00	<0.001	<0.001	0.110
IB (μmol/L), Mean ± SD	7.74 ± 2.46	<0.001	8.81 ± 3.12	<0.001	0.718	0.048	8.92 ± 3.80	<0.001	0.118	0.012
DB (μmol/L), Mean ± SD	1.32 ± 1.01	<0.001	2.47 ± 1.78	<0.001	<0.001	<0.001	3.91 ± 5.87	<0.001	<0.001	<0.001
EDDS, Mean ± SD	3.63 ± 3.01	<0.001	5.81 ± 4.27	0.169	0.020	0.011	7.54 ± 4.56	0.112	<0.001	<0.001
EDDS≥10 (%), Percentage	5.10		22.22			0.013^f	33.33			<0.001^p

Based on Bonferroni correction for EEDS scores of multiple groups compared in pairs, the P values between efficient and control groups, inefficient and control groups, efficient and inefficient groups were 0.020, <0.001 and 0.182, respectively.

The P value from Chi-square analysis to compare EEDS≥10 percentages of efficient and inefficient groups is 0.327^p.

Word p in the upper right corner of numbers refers to result from Person Chi-square Test and word f similarly refers to Fisher's exact Test. P value < 0.05 indicates significance for statistical analysis. Abbreviations in the table is similar as Table 1.

3. Results

A total of 164 pregnant women were included in the analyses, 123 of whom were followed up and their information was complete. In Table 1, no significant characteristic difference between them, including age, body mass index, education levels, parity, living habits (current smoker and current alcohol consumption), and use of assisted reproductive technology. The difference in biochemical indexes (TBA, ALT, AST, GGT, ALP, IB and DB) reflected the influence of bile duct and hepatobiliary function in ICP women (P value < 0.05). Especially, TBA$\geq$10 μmol/L was the main biochemical criteria to ICP diagnosis. The women were assessed for Edinburgh during pregnancy depression scale and Edinburgh postnatal depression scale, then the mental scale score$\geq$10 was considered potential depression [11]. During and after pregnancy, women in the ICP group had higher mental scale scores and larger potential depression percentages than others in the control group (P value < 0.05). It meant that women in the ICP group were more depressed than those in the control group. There might be a short-term effect on the psychology of ICP women, like "inertia force". However, change scale scores of EDDS to EPDS were not significantly different. Leaving the hospital reduced depression, and it was same in the ICP group.

To explore relationship between UDCA therapy efficiency and the mental scale score, we re-enrolled 41 ICP women who had been excluded because of no their follow-up data (referring to EPDS at 6th week after childbirth). In Table 2, no significant characteristic difference between various ICP and control groups, including age, body mass index, education levels, parity, and living habits (current smoker and current alcohol consumption). Increasing the number of participants might lead to difference in index (use of assisted reproductive technology). Women in efficient and inefficient groups had been significant clinical characteristics (TBA, ALT, AST, ALP, HDL, IB and DB), comparing with women in the control group (P value < 0.05). It was worth mentioning that GGT was an exception, which had no difference between inefficient and control groups. During pregnancy, women in the efficient and inefficient groups had higher mental scale scores and larger potential depression percentages than others in the control group (P value < 0.05). Statistical approach needed an improved method to judge differences of score values when multiple groups were compared in pairs, so Bonferroni correction was used to counteract the error of multiple comparisons. Then we got P values between efficient and control groups, inefficient and control groups, efficient and inefficient groups were 0.020, $<$0.001 and 0.182, respectively. There was no statistically significant difference between the efficient and inefficient groups, meaning that UDCA could be efficient for falling the TBA to normal level in serum after a previous rise, but not decrease the mental scale scores of ICP women and fail to ease a depressive tendency through this drug treatment. It was worth mentioning that when EDDS$\geq$10, the odds ratio of the inefficient group has a higher value than the efficient group (Table 3).

4. Discussion

The bile acid is a communication channel to link gut and brain, when some key primary bile acids excreted in intestine are modified by gut microbiota, carried into the brain through the circulatory system and playing their roles variously on psychological function in brain [5]. The ICP women have the high TBA concentration in their blood, which originates from the cholestasis in the liver. This might lead to an increase in depressive tendency and depression incidence (P value $= 0.001$, Table .1). The disease is usually treated with UDCA [12], that is a tertiary bile acid normally from bacterial modification but is insufficient in the ICP women. This drug can improve maternal symptoms (including pruritus) and biochemical abnormalities (including serum TBA, serum transaminases, serum bilirubin and so on) [6]. In the last century, a classical experiment on the UDCA impairment function in bile acid transport across the placenta have showed that this drug even could restore the ability of the placenta to carry out vectorial bile acid transfer [13]. However, the UDCA efficient group had no statistical significance on mental scale scores, compared with the inefficient group (P value $= 0.182$, Table 2). There was also no statistical difference in the numbers of depression women from the efficient and inefficient groups (P value $= 0.327$, Table 2). When EDDS$\geq$10, the odds ratio of the inefficient group has a higher value than the efficient group (9.30 vs. 5.31, Table 3), indicating that the risk of major depression is greater in the UDCA-inefficient women. It is powerful clinical evidence that the UDCA treatment can decrease the TBA concentration in serum but fail to recover the bile acid function as a communication bridge between gut microbiota and brain, while cholestasis in liver is making intestinal bile reduced and not modified enough in order to effect on brain function. The gut microbiota play an important role in the circulation of bile acids, and ultimately in the composition of bile acids in the blood [3,7], which worsened perinatal depressive tendency.

Table 3
The odds ratios for this further study with the retrospective data of various ICP and control groups.

Therapeutic effect	Number	95% Confidence interval	Odds ratio (95% Confidence interval)
Control group & EDDS$\geq$10, N	5	10.32–14.48	
Control group & EDDS$<$10, N	93	2.84–3.71	
Efficient group & EDDS$\geq$10, N	6	8.80–14.53	
Efficient group & EDDS$<$10, N	21	2.81–5.48	
EDDS$\geq$10: Efficient group vs. Control group			5.31 (1.48–19.12)
Inefficient group & EDDS$\geq$10, N	13	11.72–14.44	
Inefficient group & EDDS$<$10, N	26	3.85–5.69	
EDDS$\geq$10: Inefficient group vs. Control group			9.30 (3.03–28.50)

The values of 95% Confidence interval are from EEDS scores. Odds ratio (95% Confidence interval) was calculated by the Woolf version of confidence interval.
N means number; & means and; Vs. means versus.

The study on serum nontarget metabolome shows that the bile, taurine and hypotaurine metabolite pathways are altered in the ICP women [14]. Though characteristics of bile acids are constantly changing in the second and third trimesters of normal pregnancy [15], the composition of bile acids from the ICP women are specifically different from the health [16,17]. The bile acids in circulatory system can cross the blood-brain barrier, either by simple diffusion [18] or through their transporters [5]. Bile acids in the brain are not only derived from peripheral blood, but also are synthesized in the brain, with a brain specific cytochrome P450 46A1 (CYP46A1, initiating 24S-hydroxycholesterol in turn via a series of intermediates to CDCA) [19]. There are different conjugated and unconjugated bile acids in the brain, playing their respective roles [20]. Bile acids are ligands to affect the brain through the MGB axis, which is a complex physiological process. They have a variety of molecular structures, meaning their cellular receptors are correlated with different binding forces [5]. For working on the brain, bile acids are potentially linked to some mental illnesses [21]. Major depressive disorder and anxiety are associated to the change of bile acid compositions from gut microbiota [22]. Some secondary bile acids have abnormal function to cause chronic stress, a depressive-like state [23].

Of course, there are still some aspects that could be further studied, with increased data and improved methods in future. As a low-incident disease, there is less concentration on complicated mental illness, leading to less clinical psychology studies about ICP, so we will plan to work on collecting more clinical data in subsequent years. It is worth mentioning that as the subsequent collection of clinical data, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) should also be considered as effective data, as ADH I has been proved to become a higher level dramatically in the ICP disease [24]. With the development of separation and identification techniques for complex biological samples, quantitative data on various bile acids will become more reliable and there will be more interesting findings on connections between bile acids and the brain.

5. Conclusion

With this follow-up study of 25 ICP women and this retrospective study of 66 ICP women, there is an interesting finding that ICP disease increased mental scale scores but using UDCA as a conventional treatment could not decrease scores, suggesting UDCA could not replace the function of gut microbiota for recovering the changed composition in bile acids and easing the worsened depression through the MGB axis. This interesting finding could lead to a new clinical guideline for the ICP treatment in future. Given the limitation of the study, we will have to do further work later such as conducting a multi-center study, exploring treatment options and testing clinical samples.

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Author contribution statement

Hualin Xu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yupin Xu: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Guoqiang Zhao: Contributed reagents, materials, analysis tools or data.

Xukun Fu: Performed the experiments.

Hongmei Lin: Conceived and designed the experiments; Performed the experiments.

Data availability statement

Data will be made available on request.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e15845.

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