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BRIEF COMMUNICATION

Inflammatory cytokines expression in Wilson's disease

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Abstract

Background Wilson's disease (WD) is an autosomal recessive inherited disorder of copper (Cu) metabolism. Inflammation is a self-defensive reaction aimed at eliminating or neutralizing injurious stimuli, and restoring tissue integrity. Copper deposition may lead to inflammation in the organs and tissues of WD patients.

Objective The aim of this study was to compare the plasma levels of inflammatory cytokines in patients with WD and healthy group, and also to assess whether inflammatory cytokines affects the clinical manifestation of WD.

Methods Ninety-nine patients with WD and 32 controls were recruited for this study. Ray Biotech antibody microarray was used to detect the levels of plasma inflammatory cytokines.

Results and conclusion Our results showed significant increase in T helper (Th) 1 cells (IL-2, TNF-α, and TNF-β), Th2 cells (IL-5, IL-10, and IL-13), and Th17 (IL-23) ($p < 0.05$). Higher plasma Th 1 cells (IL-2, TNF-α, and TNF-β), Th 2 cells (IL-13), and Th 17 (TGF-β1, IL-23) levels were found in neurological patients compared with control groups ($p < 0.01$). Besides, we found Th 1 cells (TNF-α and TNF-β), Th 3 (TGF-β1), and Th 17 (IL-23) levels were significantly higher in hepatic and neurological patients ($p < 0.05$). In addition, the higher Th1 cells (IL-2, TNF-α, and TNF-β), Th2 cells (IL-13), and Th17 (TGF-β1, IL-23) and the course of WD were associated with the severity of the neurological symptoms for WD patients. Altogether, our results indicated that dysregulation of cytokines, mainly increased expression of cytokines and chemokines, occurred in WD patients.

Keywords Wilson's disease · Inflammation · Cytokine · Copper

Introduction

Wilson's disease (WD) is an inherited disorder of chronic copper toxicosis characterized by excessive copper deposition in the body, primarily in the liver and the brain [1]. It is caused by a mutation in ATP7B, a copper-transporting ATPase [2, 3]. The copper deposition results in organ damage and the clinical manifestations of WD [4]. Copper was reported to induce IL-6 secretion in a cell culture system composed of human keratinocytes and firoblasts [5]. Medici [6] found that hepatic Cu overload was associated with inflammation, which was manifested by histopathology and the elevating levels of serum alanine aminotransferase (ALT) and liver tumor necrosis factor alpha (TNF-α). Copper has been indicated to potentiate the effects of cholesterol on inflammation-induced Aβ neurotoxicity through increased TNF production [7]. In humans, Copper accumulates in the brain and causes brain damage, giving rise to neurological symptoms in some WD patients. However, the mechanism of tissue damage from copper deposition is sinuousness and not adequately understood. As is well-known that increased extracellular copper contribute to neuronal pathogenic process by increasing the production of

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dangerous radical oxygen species, but the other molecular mechanisms of copper neurotoxicity has been rarely investigated yet. Spisni [8] found that the increased extracellular Cu levels strongly affected the secretions of IL-1a, IL-12, and Rantes. Cu was capable of shifting GN11 and primary neurons towards an inflammatory state. Copper accumulated and inflammatory markers were increased in striatum of toxic milk mice, which is the rodent model for WD [9].

Inflammation is a normal, albeit, nonspecific response of the brain's immune system to harmful stimuli such as tissue damage or pathogen invasion. Inflammatory reaction is observed in many brain disorders, especially in those with a neurodegenerative course such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease [10]. An acute or short-term neuroinflammatory response is likely important for a healthy functioning brain and contributes to the repair of damaged or infected tissue. However, when the inflammatory process continues for a long period of time (weeks, months, or even years), damage to the surrounding brain tissue may become substantial [11]. Pro-inflammatory cytokines, such as granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), macrophage inflammatory protein (MIP), and tumor necrosis factor, have been shown to increase synaptic transmission and to induce excitotoxic neuronal damage [12–16]. Consequently, the result of most related studies endorsed very important role of cytokine profile in neurodegeneration onset and its clinical progress.

Since the susceptibility to neuroinflammation may contribute to the severity of both the WD disease symptoms and phenotypic manifestations, the aim of the present study was to evaluate plasma levels of inflammatory cytokines in WD patients in comparison with healthy controls to find probable association between cytokine cytokine and WD.

Materials and method

Patients and controls

A control group consisted of 32 age- and gender-matched healthy individuals, whose serum ceruloplasmin and copper were in the normal level and did not diagnose WD. A total of 99 patients were prospectively recruited in this study from September 2012 to March 2014 at The Institute of Neurology, Affiliated Hospital, Anhui University of T.C.M. According to the type of presentation, symptomatic patients were classified into three groups:

- Group 1 (G1): patients with hepatic presentation defined as presence at time of diagnosis of exclusively hepatic symptoms and signs in the absence of neurological symptoms and signs as confirmed by careful neurological examination ($n = 38$).
- Group 2 (G2): 39 patients with neurological presentation defined as the presence of neurological symptoms ($n = 39$).
- Group 3(G3): 22 patients with hepatic and neurological presentation defined as the presence of hepatic and neurological symptoms ($n = 22$).

The diagnosis of WD was based on the Leipzig scoring system (Table 1). The Leipzig scoring system, which was proposed by an international consensus of experts, provides a good diagnostic accuracy. It is the combination of clinical and family history, physical examination, and certain key laboratory tests that collectively establish the diagnosis. The severity of WD measured using the Global Assessment Scale for Wilson's disease (GAS for WD) (Appendix) [17]. The GAS for WD has two Tier scale. Tier 1: Global Disability covers 4 domains including Liver, Cognition and behavior, Motor, and Osseomuscular. Tier 2: Neurological Assessment assesses different aspects of neurological dysfunction due to WD in detail under 14 items. The participants were also assessed with extensive medical, neurological, social and family interviews, and laboratory blood analyses. Age- and gender-matched healthy individuals were recruited as controls ($n = 24$).

Preparation of blood samples

We drew blood from 99 WD patients and 32 healthy controls. After collection, venous blood samples were centrifuged within 20 min of collection, at 2500 g for 10 min, and the supernatant plasma was then transferred into polypropylene tubes at − 86 °C until the assays were determined.

Cytokine, ceruloplasmin, and serum copper assay

Plasma inflammatory cytokine levels were measured by Ray Biotech's antibody microarray. Ceruloplasmin was measured using immunonephelometry. Serum copper concent ration were performed using the atomic absorbance spectroscopy technique.

Statistical analysis

All data were statistically analyzed by SPSS 17.0. Data were expressed as mean ± standard deviations (SD). ANOVA analysis and multiple comparisons were used to compare the plasma levels of inflammatory cytokines between control group and three WD groups and we used post hoc correction if there were significant differences, while categorical variables were compared by chi-square test. Multiple linear regression was used for the relationship between the serum ceruloplasmin, serum copper, course of the disease, age, inflammatory

Table 1 Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001

Typical clinical symptoms and signs		Other tests	
K-F rings		Liver copper (in the absence of cholestasis)	
Present	2	> 5 × ULN (> 4 μmol/g)	2
Absent	0	0.8–4 μmol/g	1
Neurologic symptoms**	Normal (< 0.8 μmol/g)	− 1	
Severe	2	Rhodanine-positive granules*	
Mild	1	Urinary copper (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin	1–2 × ULN	1	
Normal (> 0.2 g/L)	0	> 2 × ULN	2
0.1–0.2 g/L	1	Normal, but >5 × ULN after D-penicillamine	2
< 0.1 g/L	2	Mutation analysis	
Coombs-negative hemolytic anemia	On both chromosomes detected	4	
Present	1	On 1 chromosomes detected	1
Absent	0	No mutations detected	0
Total score	Evaluation		
4 or more	Diagnosis established		
3	Diagnosis possible, more tests needed		
2 or less	Diagnosis very unlikely		

*If no quantitative liver copper available, **typical abnormalities at brain magnetic resonance imaging

KF Kayser-Fleischer, *ULN* upper limit of normal

cytokines, and the severity of disease. $p < 0.05$ was considered to be significant.

Results

This study was based on 32 healthy controls and 99 consecutive WD subjects; 38 hepatic WD patients, 39 neurologic WD patients, and 22 hepatic and hepatic WD siblings. The baseline characteristics and clinical findings of both study groups are shown in Table 2. The mean age, serum copper, and serum ceruloplasmin were presented as mean ± standard deviation. No significant difference was found in age and gender among all patient subgroups and control groups.

Copper and ceruloplasmin levels

The mean serum copper of patients with hepatic WD was 3.6 ± 2.0 μmol/L, while the mean serum ceruloplasmin was 66.7 ± 38.6 μg/mL. The mean serum copper of patients with neurological WD was 3.2 ± 1.5 μmol/L, and the mean serum ceruloplasmin was 43.7 ± 16.8 μg/mL. The mean serum copper of patients with hepatic and neurological WD was 2.9 ± 1.1 μmol/L, while the mean serum ceruloplasmin was 50.2 ± 20.5 μg/mL.

Table 2 Comparison between WD patients and control group

	Control ($n = 32$)	Group 1 ($n = 38$)	Group 2 ($n = 39$)	Group 3 ($n = 22$)
Gender (male/female)	14/18	15/23	20/19	12/10
Age (years)	26.9 ± 10.9	18.9 ± 12.7	21.4 ± 7.2	27.5 ± 8.6
Course of the disease (years)	–	4.8 ± 6.6	4.8 ± 5.2	10.6 ± 7.8
K-F ring positive	–	24	16	7
Ceruloplasmin (μg/mL)	246.5 ± 51.9	66.7 ± 38.6	43.7 ± 16.8	50.2 ± 20.5
Serum copper (μmol/L)	12.5 ± 4.0	3.6 ± 2.0	3.2 ± 1.5	2.9 ± 1.1
ALT(u/L)	22.28 ± 8.55	111.03 ± 81.18	31.25 ± 7.63	90.71 ± 65.45
AST(u/L)	24.28 ± 6.91	88.76 ± 63.25	33.33 ± 6.27	74.52 ± 44.02

M male, *F* female, *CP* ceruloplasmin

* ANOVA analysis, chi-square test, correction for multiple comparisons

Cytokine levels

In the present study, plasma levels of T helper (Th) 1 cells (IL-2, TNF-α, and TNF-β), Th 2 cells (IL-5, IL-10, and IL-13), and Th 17 (IL-23) were found to be markedly higher in patients with hepatic WD than in the control groups ($p < 0.05$; Fig. 1). However, there were no significant difference in the Th 1 cells (IFN-γ, IL-12p70, and IL-22), Th 2 cells (GM-CSF, IL-4, IL-6, and IL-21), Th 3 (TGF-β1), Th 17 (IL-17 and IL-17F), IL-1β, MIP-3a, and IL-28A between hepatic patients and healthy controls ($p > 0.05$; Fig. 1). Higher plasma Th 1 cells (IL-2, TNF-α, and TNF-β), Th 2 cells (IL-13), Th 3 (TGF-β1), and Th 17 (IL-23) levels were found in neurological patients compared with control groups ($p < 0.05$; Fig. 1). Nevertheless, there were no significant differences in the Th 1 cells (IFN-γ, IL-12p70, and IL-22), Th 2 cells (GM-CSF, IL-4, IL-5,IL-6, IL-10, and IL-21), Th 17 (IL-17 and IL-17F), IL-1β, MIP-3a, and IL-28A between neurological patients and healthy controls ($p > 0.05$; Fig. 1). Meanwhile, we found Th 1 cells (TNF-α and TNF-β), and Th 17 (TGF-β1, IL-23) levels were significantly higher in hepatic and neurological patients ($p < 0.05$; Fig. 1). However, There were no significant differences in the Th 1 cells (IL-2, IFN-γ, IL-12p70, and IL-22), Th 2 cells (GM-CSF, IL-4, IL-5,IL-6, IL-10, IL-13, and IL-21), Th 17 (IL-17 and IL-17F), IL-1β, MIP-3a, and IL-28A between hepatic and neurological patients and healthy controls ($p > 0.05$; Fig. 1).

Correlations between cytokines, copper, CP, course of the disease, age, and severity of WD

We did not find statistically significant correlation between serum CP, serum copper, course of the disease, age, and IL-2, IL-13, IL-23, and TNF-α for hepatic patients ($p > 0.05$). There were linear relationships between course of the disease and the plasma levels of IL-5 and IL-10 for hepatic patients ($B = 14.362$, $p = 0.022$; $B = 1.789$, $p = 0.024$). Besides, there was linear relationships between age and the plasma levels of TNF-β for hepatic patients ($B = 18.255$, $p = 0.005$). No linear relationships between serum CP, serum copper, course of the disease, age, and the plasma levels of IL-2, IL-13, TNF-α, and TNF-β for neurological patients were observed ($p > 0.05$). There were linear relationships between serum CP and IL-23 and TGF-β1 in neurological patients ($B = -34.043$, $p = 0.019$; $B = -155.144$, $p = 0.032$). According to standard partial regression coefficient, serum CP was the main variable that influences the levels of IL-23 and TGF-β1. We did not discover linear relationships between serum CP, serum copper, course of the disease, age, and the plasma IL-23, TGF-β1, TNF-α, and TNF-β for hepatic and neurological patients ($p > 0.05$).

We also discovered no linear relationships between serum CP, serum copper, course of the disease, age, the plasma level of inflammatory cytokines, and GAS1 for hepatic patients ($p > 0.05$). There were linear relationships between serum CP, serum copper, course of the disease, IL-2, IL-5, IL-10, IL-13, IL-23, TNF-α, and GAS2 for hepatic patients ($p = 0.001$, $p = 0.000$, $p = 0.006$, $p = 0.001$, $p = 0.000$, $p = 0.034$). Meanwhile, the plasma level of IL-2, IL-5, IL-10, IL-13, IL-23, and TNF-α ($B = 0.033$, $p = 0.000$; $B = 0.013$, $p = 0.000$; $B = 0.073$, $p = 0.003$; $B = 0.060$, $p = 0.000$; $B = 0.002$, $p = 0.000$; $B = 0.004$, $p = 0.025$) were the main variables that influence GAS2 for hepatic patients. We did not find statistically significant linear relationships between serum CP, serum copper, course of the disease, age, the plasma level of inflammatory cytokines, and GAS1 for neurological patients ($p > 0.05$). There were linear relationships between serum CP, serum copper, course of the disease, IL-2, IL-13, IL-23, TGF-β1, TNF-α, TNF-β, and GAS2 for neurological patients ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$). According to standard partial regression coefficient, the plasma level of IL-2, IL-13, IL-23, TGF-β1, TNF-α, TNF-β, and course of the disease ($B = 0.040$, $p = 0.000$; $B = 0.055$, $p = 0.000$; $B = 0.002$, $p = 0.001$; $B = 0.001$, $p = 0.000$; $B = 0.007$, $p = 0.000$; $B = 0.015$, $p = 0.000$; $B = 0.407$, $p = 0.003$) were the main variables influence GAS2 for neurological patients. Besides, serum CP and serum copper ($B = 0.046$, $p = 0.035$; $B = -0.893$, $p = 0.025$) were the main variable impact GAS1 for hepatic and neurological patients. There were no linear relationships between serum CP, serum copper, course of the disease, the plasma level of inflammatory cytokines, and GAS2 for hepatic and neurological patients were found ($p > 0.05$).

Discussion

WD is caused by abnormal copper metabolism in the liver due to a mutation in the copper-transporting protein ATP7B, which lead to liver damage and hepatitis [1]. Copper secondarily deposits in brain and causes brain damage. The way in which copper deposition causes brain damage is unknown. It was reported that reactive oxygen species (ROS), nitric oxide species (NOS), cytokines, and other inflammatory mediators are activated by glial cells, when the microenvironment in the CNS is changed by injuries such as trauma, infection, or ischemic attack [18]. It was reported that Cu induced IL-6 secretion in a cell culture system composed of human keratinocytes and fibroblasts [19]. Previous studies have strongly suggested that Copper deposited in striatum of the rodent models for WD, and IL-6, IL-8, IL-10, and TNF-α were increased in this area. Inflammatory response in the different area seems to follow the extent of copper accumulation [9]. The present

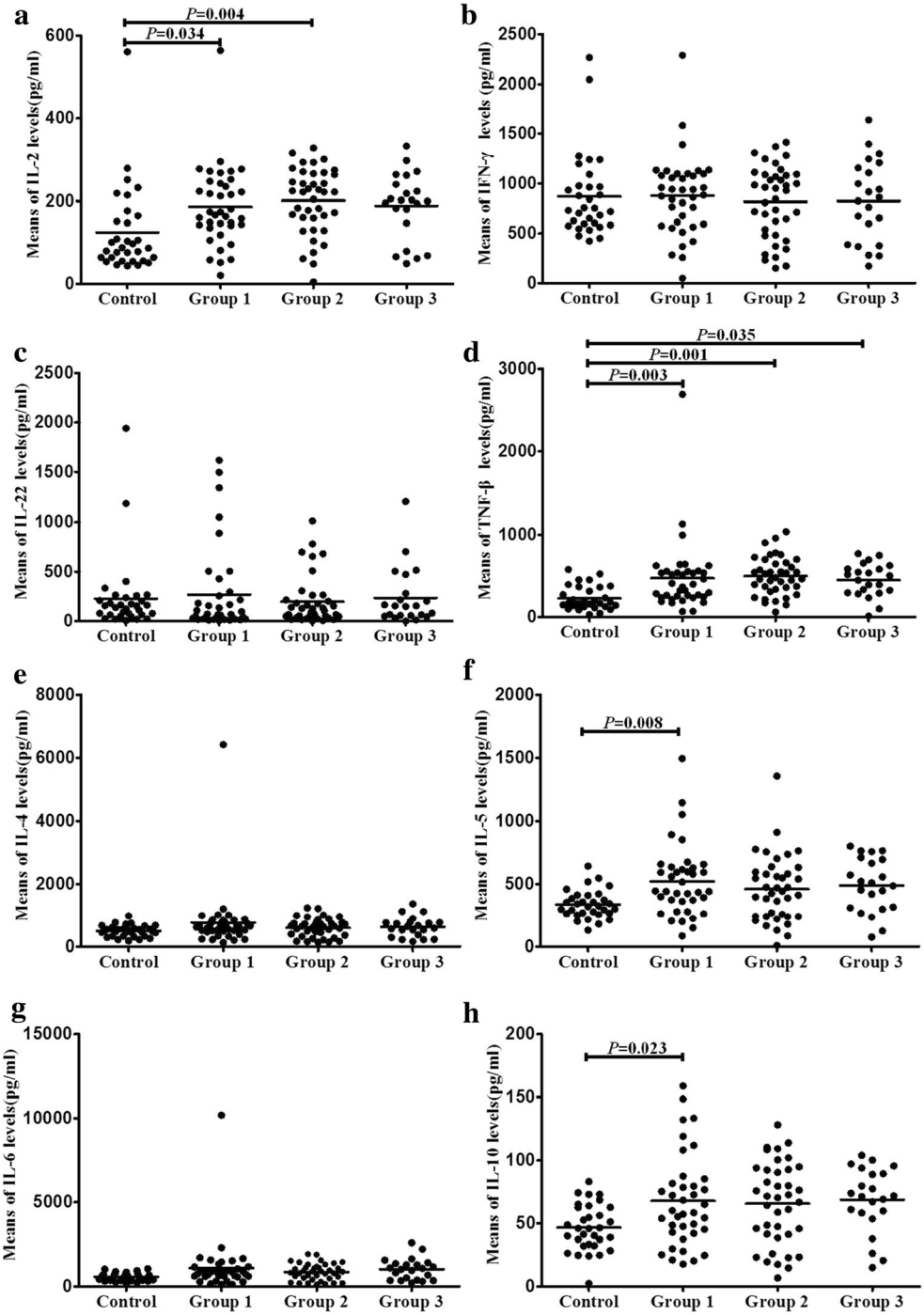

Fig. 1 Means of plasma inflammation cytokines levels were shown. Higher levels of TNF-β (D), TNF-a (L), and IL-23 (O) were found in G1, G2, and G3 groups compared with controls. Higher plasma IL-2(A), IL-13(J), and TGF-β1(T) levels were found in G1 and G2 groups compared with controls. Higher plasma IL-5(F) and IL-10(H) levels were found in G1 group compared with controls. There was no significant difference in the plasma IFN-γ(B), IL-22(C), IL-4(E), IL-6(G), GM-CSF(I), IL-21(K), IL-17(M), IL-17F(N), IL-28A(P), IL-1β(Q), IL-12p70(R), and MIP-3a(S) levels between patients and healthy controls. WD Wilson's disease. Group 1 = hepatic WD; group 2 = neurologic WD; group 3 = hepatic and neurologic WD

study for the first time reports an alteration in plasma levels of T helper (Th) 1 cells (IL-2, TNF-α, and TNF-β), Th 2 cells (IL-5, IL-10, and IL-13), and Th 17 (IL-23) in patients with WD. Interestingly, serum CP was the main variable influence the levels of IL-23 and TGF-β1. While the precise reason for this phenomenon remained unclear, its possibility has to be approached experimentally further.

Several studies have proved that continued inflammatory changes can aggravate inflammatory or non-inflammatory diseases of the CNS such as multiple sclerosis, meningitis,

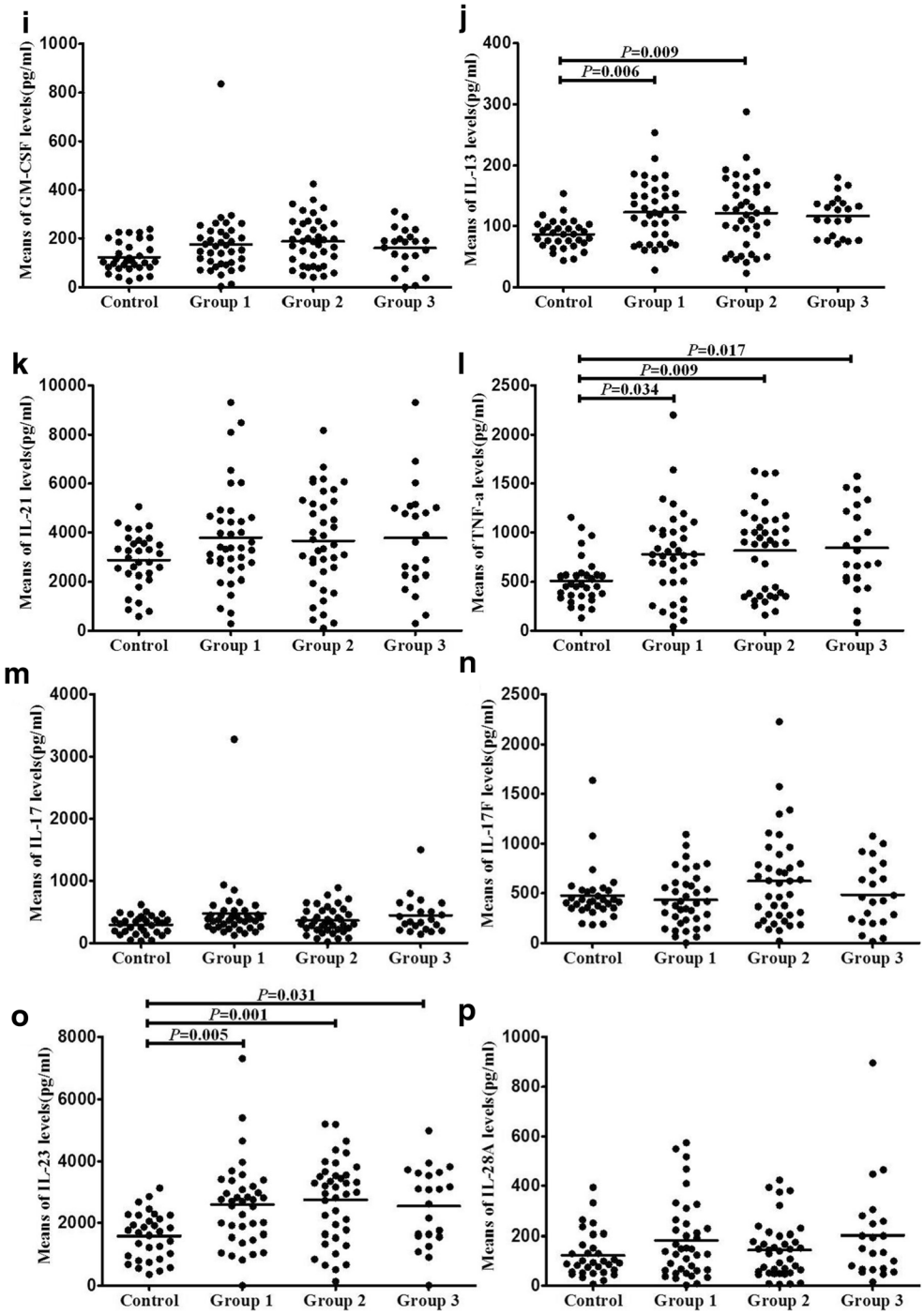

Fig. 1 continued.

Alzheimer's disease, Parkinson's disease, or Huntington's disease [20–24]. Tansey [25] demonstrated that the expression of inflammatory cytokines and chemokines brings about the induction of apoptosis in various types of brain cells, including oligodendrocytes and astrocytes. Kalita J et al. *observed* that reduction in antioxidants and increase in oxidative stress markers, cytokines, and glutamate are more marked in symptomatic neurologic WD than asymptomatic patients [26]. In the rodent model for WD, a fulminant hepatitis is surveyed which may led to increased levels of cytokines in the blood, including TGF-β and TNF-α [9]. Peripheral inflammatory responses can affect brain functioning. For instance, Choo et al. [27] observed that systemic inflammation is strongly linked to the decline of cognitive in Alzheimer's disease. Weberpals et al. [28] demonstrated that systemic inflammation can induce long-term memory deficits in mice and synaptic damage. In the present study,

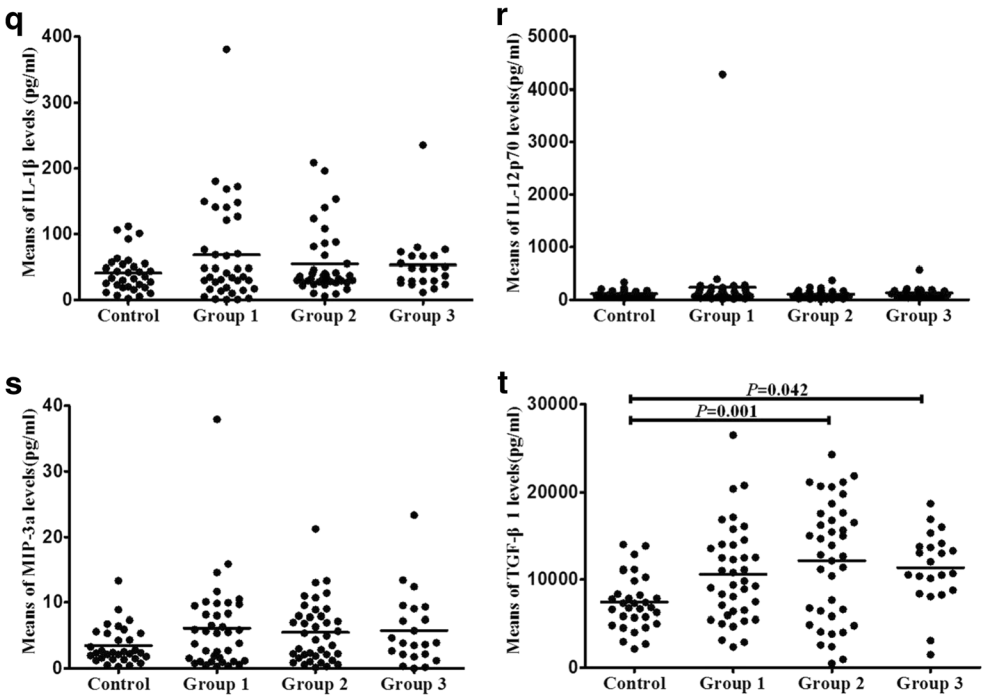

Fig. 1 continued.

we demonstrate for the first time that the plasma levels of IL-2, IL-5, IL-10, IL-13, IL-23, and TNF-α were the main variables that influence GAS2 for hepatic patients. These inflammatory cytokines can enter into CNS not only directly through the circumventricular organs and open the blood–brain barrier. The resulting translocation of inflammatory cytokines may disturb neuronal and glial homeostasis, leading to cognitive and behavioral manifestations. Neuroinflammation is believed to play an important role in the pathophysiology of WD [29] and the ability of the human body to deal with increased inflammatory cytokines may be one of the factors contributing to the severity of WD. We obtained evidence that the plasma level of IL-2, IL-13, IL-23, TGF-β1, TNF-α, and TNF-β were the main variables that influence GAS2 for neurological patients. It is becoming well established that when the brain is injured and homeostasis of the microenvironment is disturbed, microglia are activated and secrete pro-inflammatory cytokines, chemokines, and reactive oxidants [30–32]. The primary aim of the increased pro-inflammatory mediators is to defend and restore neural integrity in the injured CNS. However, uncontrolled and prolonged inflammatory alterations have pernicious effects and further aggravate the neuronal lesion. Pro-inflammatory cytokines primarily mediate and facilitate neural activities and inflammatory processes. Particularly during the early period of development, activated pro-inflammatory cytokines may exert harmful effects on the brain [10]. In patients with the neuropsychiatric form of WD, copper in CSF and post-mortem brain tissue clearly show that concentrations of copper are increased up to 85% of normal levels in the CNS [33]. Another study showed despite after several years of chelating treatment, abnormal brain copper deposits still not alleviated. Besides, the severity of neuropathological findings was related to cerebral copper content [34]. Moreover, Kalita J et al. suggested that the drecreased expression of antioxidants and the increased expression of MDA, cytokines, and glutamate are closely related to Cu homeostasis in WD [26]. The increased copper in brain result to neuronal apoptosis through oxidative stress and neuroinflammation. It is possible that copper deposition in the brain disturbes homeostasis of the microenvironment, microglias are activated and secrete inflammatary cytokines, chemokines, and reactive oxidants, and that this could account for the impaired neurological examination.

Conclusion

In conclusion, our results showed that an elevation of inflammatory cytokines occurred in WD patients. Further studies with more samples should be done to explore the role of inflammatory cytokines in WD patients. This information is helpful for suggesting inflammatory cytokines as new candidates in diagnostic and therapeutic approaches. In addition, the plasma levels of inflammatory cytokines showed a significant linear relationship with the disease severity of WD patients. While regulated neuroinflammation is an important neuroprotective mechanism in the CNS, unregulated, chronic neuroinflammation is toxic if not resolved as in WD. We can put the plasma inflammatory cytokines as a potential biomarker that may aid in predicting the prognosis of WD patients in further large-scale studies.

Compliance with ethical standards

Ethical statement The study was approved by the institutional review Hospital Affiliated to Institute of Neurology, Anhui University of Traditional Chinese Medicine. All patients provided written informed consent.

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References

1. Seo JK (2006) Wilson's disease: an update. Nat Clin Pract Neurol 2: 482–493
2. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW (1993) The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 5:327–337
3. Thomas GR, Forbes JR, Roberts EA, Walshe JM, Cox DW (1995) The Wilson disease gene: spectrum of mutations and their consequences. Nat Genet 9:210–217
4. Loudianos G, Lepori MB, Mameli E, Dessì V, Zappu A (2014) Wilson disease. Prilozi 35(1):93–98
5. Schmalz G, Schuster U, Schweikl H (1998) Influence of metals on IL-6 release in vitro. Biomaterials 19(18):1689–1694
6. Medici V, Shibata NM, Kharbanda KK, LaSalle JM, Woods R, Liu S, Engelberg JA, Devaraj S, Török NJ, Jiang JX, Havel PJ, Lönnerdal B, Kim K, Halsted CH (2013) Wilson's disease: changes in methionine metabolism and inflammation affect global DNA methylation in early liver disease. Hepatology 57(2):555–565
7. Lu J, Wu DM, Zheng YL, Sun DX, Hu B, Shan Q, Zhang ZF, Fan SH (2009) Trace amounts of copper exacerbate beta amyloid-induced neurotoxicity in the cholesterol fed mice through TNF-mediated inflammatory pathway. Brain Behav Immun 23(2):193–203
8. Spisni E, Valerii MC, Manerba M, Strillacci A, Polazzi E, Mattia T, Griffoni C, Tomasi V (2009) Effect of copper on extracellular levels of key pro-inflammatory molecules in hypothalamic GN11 and primary neurons. Neurotoxicology 30(4):605–612
9. Terwel D, Löschmann YN, Schmidt HH, Schöler HR, Cantz T, Heneka MT (2011) Neuroinflammatory and behavioural changes in the Atp7B mutant mouse model of Wilson's disease. J Neurochem 118(1):105–112
10. Kim YK, Na KS, Myint AM, Leonard BE (2015) The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 64:277
11. Freeman LC, Ting JP (2015) The pathogenic role of the inflammasome in neurodegenerative diseases. J Neurochem 136: 29–38
12. Centonze D, Muzio L, Rossi S, Cavasinni F, De Chiara V, Bergami A, Musella A, D'Amelio M, Cavallucci V, Martorana A, Bergamaschi A, Cencioni MT, Diamantini A, Butti E, Comi G, Bernardi G, Cecconi F, Battistini L, Furlan R, Martino G (2009) Inflammation triggers synaptic alteration and degeneration in experimental autoimmune encephalomyelitis. J Neurosci 29:3442–3452
13. Rossi S, Furlan R, De Chiara V, Motta C, Studer V, Mori F, Musella A, Bergami A, Muzio L, Bernardi G, Battistini L, Martino G, Centonze D (2012) Interleukin-1 β causes synaptic hyperexcitability in multiple sclerosis. Ann Neurol 71:76–83
14. Froger N, Orellana JA, Calvo CF, Amigou E, Kozoriz MG, Naus CC, Sáez JC, Giaume C (2010) Inhibition of cytokine-induced connexin43 hemichannel activity in astrocytes is neuro- protective. Mol Cell Neurosci 45:37–46
15. Lai AY, Swayze RD, El-Husseini A, Song C (2006) Interleukin-1 beta modulates AMPA receptor expression and phosphorylation in hippocampal neurons. J Neuroimmunol 175:97–106
16. Tolosa L, Caraballo-Miralles V, Olmos G, Lladó J (2011) TNF-α potentiates glutamate-induced spinal cord motoneuron death via NF-kB. Mol Cell Neurosci 46:176–186
17. Aggarwal A, Aggarwal N, Nagral A, Jankharia G, Bhatt M (2009) A novel global assessment scale for Wilson's disease (GAS for WD). Mov Disord 24(4):509–518
18. Di Filippo M, Chiasserini D, Tozzi A, Picconi B, Calabresi P (2010) Mitochondria and the link between neuroinflammation and neurodegenertion. J Alzheimers Dis 20:369–379
19. Schmalz G, Schuster U, Schweikl H (1998) Influence of metalson IL-6 release in vitro. Biomaterials 19(18):1689–1694
20. Aktas O, Ullrich O, Infante-Duarte C, Nitsch R, Zipp F (2007) Neuronal damage in brain inflammation. Arch Neurol 64:185–189
21. Heneka MT, O'Banion MK (2007) Inflammatory processes in Alzheimer's disease. J Neuroimmunol 184:69–91
22. Hirsch EC, Hunot S (2009) Neuroinflammation in Parkinson, s disease: a target for neuroprotection? Lancet Neurol 8:382–397
23. Bjorkqvist M, Wild EJ, Tabrizi SJ (2009) Harnessing immune alterations in neurodegenerative diseases. Neuron 64:21–24
24. Verkhratsky A, Parpura V, Pekna M, Pekny M, Sofroniew M (2014) Glia in the pathogenesis of neurodegenerative diseases. Biochem Soc Trans 42:1291–1301
25. Tansey M, Tran T, Lee JK (2009) Neuroinflammation in Parkinson's disease. J NeuroImmune Pharmacol 4:419–429
26. Kalita J, Kumar V, Misra UK, Ranjan A, Khan H, Konwar R (2014) A study of oxidative stress, cytokines and glutamate in Wilson disease and their asymptomatic siblings. J Neuroimmunol 274(1–2):141–148
27. Choo XY, Alukaidey L, White AR, Grubman A (2013) Neuroinflammation and copper in Alzheimer's disease [J]. Int J Alzheimers Dis 2013:145345
28. Weberpals M, Hermes M, Hermann S, Kummer MP, Terwel D, Semmler A, Berger M, Scha fers M, Heneka MT (2009) NOS2 gene deficiency protects from sepsis-induced long-term cognitive deficits. J Neurosci 29:14177–14184
29. Videla LA, Fernández V, Tapia G, Varela P (2003) Oxidative stress-mediated hepatotoxicity of iron and copper: role of Kupffer cells. Biometals 16(1):103–111
30. Harry GJ, Kraft AD (2008) Neuroinflammation and microglia: considerations and approaches for neurotoxicity assessment. Expert Opin Drug Metab Toxicol 4(10):1265–1277
31. Lehnardt S (2012) Innate immunity and neuroinflammation in the CNS: the role of microglia in Toll-like receptor-mediated neuronal injury. Glia 58:253–263
32. Streit WJ, Walter SA, Pennell NA (1999) Reactive microgliosis. Prog Neurobiol 57(6):563–581
33. Kodama H, Okabe I, Yanagisawa M, Nomiyama H, Nomiyama K, Nose O, Kamoshita S (1988) Does CSF copper level in Wilson disease reflect copper accumulation in the brain? Pediatr Neurol 4(1):35–37
34. Horoupian DS, Sternlieb I, Scheinberg IH (1988) Neuropathological findings in penicillamine-treated patients with Wilson's disease. Clin Neuropathol 7(2):62–67