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Association of serum gamma-glutamyltransferase and C-reactive proteins with neuromyelitis optica and multiple sclerosis

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ABSTRACT

Background: Many studies have demonstrated that serum gamma glutamyltransferase (GGT) within normal range might be an early marker of oxidative stress. However the role of GGT in neuromyelitis optica (NMO) and multiple sclerosis (MS) is unknown.
Methods: We assessed the correlations among GGT and C-reactive protein (CRP) levels, as well as clinical characteristics of NMO and MS. Serum GGT and CRP levels were measured in 106 NMO patients, 87 MS patients, 79 patients with non-inflammatory neurological diseases (Parkinson disease) and 80 healthy controls (HC). Clinical parameters, blood-brain barrier (BBB) index and Delpech index of MS and NMO were also investigated.
Results: We found that NMO patients had higher serum GGT and CRP levels within their normal ranges compared to MS, PD, healthy controls. NMO patients exhibited significantly higher EDSS scores than MS patients. The BBB index in NMO patients was significantly higher than that in MS patients. Significant correlations existed between serum GGT and CRP levels and EDSS scores, BBB index in NMO and MS patients.
Conclusion: Elevated GGT and CRP levels within their normal ranges in NMO and MS may be associated with inflammatory response, oxidative stress and BBB disturbance in the diseases. Further study into the underlying pathophysiology of this relationship is warranted.

1. Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system (CNS) that can cause severe optic neuritis and myelitis (Kira, 2011). Multiple sclerosis (MS) is also an inflammatory demyelinating disease of the CNS (Kira, 2003). In Asia, NMO is more common than MS. The distinction between NMO and MS has long been unclear. For many decades NMO was considered a variant of MS. However some studies have shown that inflammatory NMO profiles primarily present as eosinophils/neutrophils and autoantibody reactions (Correale and Fiol, 2004; Weinshenker, 2007), whereas MS has T-lymphocyte and mononuclear macrophage reactions as the primary immunopathogenesis (Barnett et al., 2006). In addition a majority of NMO patients develop auto-antibodies (NMO-IgG) against aquaporin 4 (AQP4) in the CNS (Lennon et al., 2004). As a result Weinshenker et al. suggested that NMO was distinguishable from MS in clinical, imaging, serological, and immunopathological profiles (Weinshenker, 2003).

A series of epidemiological studies (Lee et al., 2004a; Lee and Jacobs, 2005; Lee et al., 2003; Lee et al., 2004b) have suggested serum gamma glutamyltransferase (GGT) within its normal range might be an early marker of oxidative stress. C-reactive protein is proven to be a classical marker of inflammation. Lee et al. (Lee and Jacobs, 2005) argued that oxidative stress leads to an inflammatory response and elevation in GGT might occur before elevation in CRP. CRP values were similar in patients with MS and in healthy controls but higher during MS relapses than in remission (Soilu-Hanninen et al., 2005).

Although the relationship between cellular GGT and serum GGT is not known, cellular GGT has been known to play an important role in antioxidant defense systems (Kugelman et al., 1994). Paradoxically,

Abbreviations: GGT, gamma-glutamyltransferase; CRP, C-reactive protein; MS, multiple sclerosis; NMO, neuromyelitis optica; PD, Parkinson disease; EDSS, expanded Disability Status Scale; NMO-IgG, neuromyelitis optic-immunoglobulin; AQP4, aquaporin 4; BBB, blood-brain barrier

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cellular GGT may also be involved in the generation of reactive oxygen species in the presence of transition metals (Drozdz et al., 1998; Glass and Stark, 1997) and glutathione metabolized by GGT initiates an oxidative process that leads to a radical-rich environment and oxidative damage (Stark et al., 1994). In addition GGT expression regulates reactive oxygen species (ROS) in T-lymphocytes and modulates Fas-induced damage by altering NF-kappa B activity (Carlisle et al., 2003). As we know, oxidative stress appears to be a key component of many reactions associated with chronic inflammation, and chronic oxidative stress is thought to result in damage to DNA, lipids, proteins, and other molecules which may contribute to the development and progression of chronic diseases including diabetes (Xu et al., 2011), cardiovascular disease (Holvoet et al., 2007), cancer (Strasak et al., 2008), MS (Gonsette, 2008a; Gonsette, 2008b), and NMO (Penton-Rol et al., 2009). Previous studies have shown that serum GGT level was increased in some chronic diseases such as diabetes (Lee et al., 2003), cardiovascular disease (Lee et al., 2007) and cancer (Strasak et al., 2008). However little is known about GGT and CRP levels in idiopathic inflammatory CNS diseases such as NMO and MS. The present study aimed to explore the combined effects of GGT and CRP in NMO and MS.

2. Methods

2.1. Study subjects

The present study was performed at the MS Clinical Center, Department of Neurology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, P. R. China. From 2007–2011, serum samples were collected from 352 participants. In order to investigate serum GGT levels in patients with non-inflammatory neurological disorders we also enrolled Parkinson disease (PD) patients as a control group. Demographic and clinical characteristics of NMO and MS patients, as well as PD patients and healthy controls are presented in Table 1. MS was identified in accordance with McDonald's criteria (Polman et al., 2005), and NMO was defined according to Wingerchuk's criteria (Wingerchuk et al., 2006). All patients were scored using the Expanded Disability Status Scale (EDSS).

2.2. Ethics statement

The present study's protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (No.2007–33), and all participants involved in this study provided written informed consent. Consent was given both in writing and verbally for measuring the Expanded Disability Status Scale (EDSS) scores and all measurements were performed by an experienced neurologist who was blinded to the diagnostic categorization. The measurement procedure was taken as defined by Kurtzke (Kurtzke, 1983). Since those measurements benefit the therapies of NMO and MS patients involved in this study, the ethics committees also approved this consent procedure.

2.3. Anti-AQP4 antibody serum testing

Serum from 111 NMO patients was tested for the presence of anti-AQP4 antibodies using a commercial sampling kit (Euroimmun, Lübeck, Germany) in accordance with the manufacturer's instructions.

2.4. Blood-brain barrier (BBB) index and Delpech index

Samples of cerebral spinal fluid (CSF) and matched serum were obtained from MS patients and NMO patients. Three MS patients refused lumbar puncture. The concentrations of IgG and albumin (Alb) in paired serum and CSF were measured by nephelometry, and the BBB index and Delpech index were calculated according to the following formulas: BBB index formula = 1000 Alb csf/Alb serum and Delpech index formula = (IgG csf /IgG serum)/ (Alb csf/Alb serum).

2.5. Biochemical measurements

Serum GGT level and CRP level were measured using an auto-analyser (Clinical Analyzer 7180-ISE, Hitachi High Technologies, Tokyo, Japan). Venous blood samples for serum GGT measurements were obtained from all subjects. Levels of serum GGT > 50U/L were determined to be above laboratory pathology cutpoint in our hospital. Levels of serum GGT > 50U/L, and alanine transaminase (ALT) > 45 U/L were determined to abnormal liver function.

Exclusion criteria included treatment with acetylsalicylic acid, thiazide diuretics, ibuprofen, and other drugs that could influence liver enzyme levels, as well as subjects with diabetes or liver, heart, or renal disease and alcohol intake. All samples were taken before intravenous methylprednisolone (IVMP). Fulfillment of inclusion and exclusion criteria was confirmed retrospectively by a review of medical records by the neurologist specialized in demyelinating diseases.

2.6. Statistical analysis

All continuous variables were presented as the mean (± standard deviation) if the data was normally distributed or as medians (min, max) if the data was not normally distributed. The categorical variable (gender) was shown as a percentage. The effect of age on serum GGT levels for different groups was analyzed by covariance analysis. The comparison between serum GGT levels of the NMO, MS, PD, and healthy control subjects was performed using covariance analysis with age as the covariant. Since serum GGT level has been shown to be dependent on gender, patients within each group were divided into two subgroups according to gender. In order to compare serum GGT levels in NMO patients with anti-AQP4 antibody seropositive and with anti-AQP4 antibody seronegative, we also used covariance analysis with age and gender as the covariant. A Spearman's rank correlation coefficient was used to evaluate the association of age, disease duration, annualized relapse rate, EDSS score and serum GGT level in NMO and MS patients. SPSS 16.0 (Chicago IL, USA) was used for the statistical

Table 1
Demographic and clinical parameters of NMO, MS, PD and Healthy controls.

Clinical parameters	NMO (n = 106)	MS (n = 87)	PD (n = 79)	HC (n = 80)	p
Male (n, %)	20 (18.9)	32 (36.8)	41 (51.9)	33 (41.2)	–
Age (years, mean, range)	36.7 (13 – 65)	34.2 (9 – 68)	62.2 (39 – 98)	36.9 (12 – 80)	0.185
Disease Duration (months, median, range)	18 (0.1 – 240)	12 (0.2 – 420)	60 (4 – 180)	–	0.697
Annualized relapse rate (median, range)	2 (1 – 12)	2 (1 – 13)	–	–	0.805
EDSS scores (mean, range)	3.8 (1 – 8.5)	2.9 (0 – 9.5)	–	–	0.005
Serum GGT level (U/L, mean, range)	29.26 (8 – 50)	24.66 (9 – 48)	21.05 (8 – 49)	21.05 (10 – 50)	0.011
Serum ALT level (U/L, mean, range)	20.86 (8 – 45)	20.43 (7 – 41)	20.87 (7 – 40)	20.11 (10 – 44)	0.978
Serum CRP level (mg/L, median, range)	1.85 (0 – 21.2)	1 (0 – 19.6)	0.9 (0 – 5)	0.75 (0 – 13.3)	< 0.001

MS, multiple sclerosis; NMO, neuromyelitis optica; PD, Parkinson disease; HC, Healthy control, EDSS, expanded disability status scale; GGT, gamma-glutamyltransferase; ALT, alanine transaminase; CRP, C-reactive proteins. p: NMO vs MS.