Original Paper

NeuroImmunoModulation

Neuroimmunomodulation
DOI: 10.1159/000485623

Received: September 19, 2017
Accepted after revision: November 22, 2017
Published online: February 1, 2018

Lipid Metabolism in Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis

Yaqing Shu[a] Bing Qin[a] Yue Xu[b] Xiaobo Sun[a] Zheng Chen[c] Jia Wang[d] Lisheng Peng[a] Wei Qiu[a] Zhengqi Lu[a] Aimin Wu[a]

Departments of [a]Neurology, [b]Cardiovascular Medicine, [c]Stomatology, and [d]Gynecology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Keywords
Serum lipids · Autoimmune disorders · Anti-N-methyl-D-aspartate receptor encephalitis · Oxidative stress

Abstract
Objective: Lipid metabolism has been implicated in autoimmune disorders, but its relationship with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is unclear. This study examined the association of serum lipids with anti-NMDAR encephalitis. ***Methods:*** Serum lipid profiles and C-reactive protein (CRP) were evaluated in 68 patients with anti-NMDAR encephalitis, and 68 age- and sex-matched healthy controls (CTLs). Follow-up evaluations were conducted 3 months after admission in 32 of the 68 patients. Modified Rankin scale (mRS) scores and clinical and cerebrospinal fluid parameters were evaluated in all patients. ***Results:*** Compared with CTLs, patients with anti-NMDAR encephalitis had significantly lower serum high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) levels but significantly higher serum apoB levels and apoB/apoA-I ratios. Serum HDL and apoA-I were significantly and negatively associated with serum CRP levels, whereas serum aopB levels and apoB/apoA-I ratios were positively associated with age, CRP levels, and mRS scores. Follow-up evaluations revealed that serum total cholesterol, apoA-I, and HDL-C levels were significantly higher but mRS scores were significantly lower than those before treatment, and that the increased HDL-C levels were significantly and negatively correlated with decreased mRS scores. ***Conclusion:*** Serum HDL-C and apoA-I levels are reduced in the initial phase of anti-NMDAR encephalitis and recover after treatment. Further studies about the role of serum lipid in anti-NMDAR encephalitis are needed.

Background

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder that is caused by the production of antibodies against NMDARs and results in psychosis, seizures, encephalopathy, and cognitive and movement impairment [1]. It is a severe, rare, but treatable disorder, that has been most frequently reported in young

KARGER

E-Mail karger@karger.com
www.karger.com/nim

Aimin Wu, Zhengqi Lu, and Yaqing Shu
Department of Neurology, The Third Affiliated Hospital
Sun Yat-Sen University, 600 Tianhe Road
Guangzhou, Guangdong 510630 (China)
E-Mail wuaim@126.com, lzq1828@aliyun.com, and shuyaqing@126.com

women and children, and is accompanied by teratomas in various regions such as the ovaries [2, 3]. It is believed that immune cells are important effectors and regulators of inflammation and autoimmunity in anti-NMDAR encephalitis [4]. Recent studies have shown that some cases of anti-NMDAR encephalitis may have been triggered by viral infections, such as herpes simplex encephalitis [5–7].

Lipid metabolism has been implicated as being involved in inflammation and autoimmune disorders [8–13]. Low-density lipoprotein (LDL) uptake by activated microglia and infiltrating macrophages in multiple sclerosis (MS) plaques plays an important role in MS pathogenesis [12], while high-density lipoprotein (HDL) potentially inhibits the initiation and maintenance of pathogenic blood-brain barrier (BBB) injury in MS [11]. Triglyceride (TG)-mediated leukocyte activation is an alternative proinflammatory mechanism of hypertriglyceridemia that is partly associated with the generation of oxidative stress [9]. Apolipoprotein B (apoB) is the primary predictor of inflammatory markers [14], whereas apoA is a constitutive anti-inflammatory factor [13] and may be a cell specific suppressor of the inflammatory response [10].

Abnormal serum lipid levels have been associated with some autoimmune disorders, including MS [11, 15, 16], neuromyelitis optica [17, 18], systemic lupus erythematosus (SLE) [19], and diabetes [20]. Higher serum HDL cholesterol (HDL-C) has been associated with a lower level of BBB injury in MS [11], and low levels of serum apoA-I have been found in patients with neuromyelitis optica [18]. However, the role of serum lipids in anti-NMDAR encephalitis is unknown. Here, we analyzed serum lipid levels in patients with anti-NMDAR encephalitis and determined their association with clinical parameters in these patients.

Methods

Patients and Controls

We recruited patients with anti-NMDAR encephalitis who were hospitalized from July 2014 to April 2017 as well as age- and sex-matched healthy controls (CTLs) for comparison. One control participant was randomly selected and matched to the age and sex of each index case. The anti-NMDAR encephalitis diagnostic criteria [21] were used in our study: (1) the presence of ≥1 of 6 major groups of symptoms, i.e., abnormal (psychiatric) behavior or cognitive dysfunction; speech dysfunction (pressured speech, verbal reduction, or mutism); seizures; movement disorders, dyskinesia, or rigidity/abnormal posture; a reduced level of consciousness; and autonomic dysfunction or central hypoventilation; (2) positive results for cerebrospinal fluid (CSF) antibody testing (IgG anti-GluN1 antibodies); (3) a reasonable exclusion of other disorders.

Serum and CSF samples from all patients with anti-NMDAR encephalitis were analyzed as described in our previous paper [22]. Briefly, the samples were analyzed by indirect immunostaining using a commercially available kit (Euroimmun, Lübeck, Germany) to detect IgG antibodies against NMDAR.

Brain magnetic resonance imaging (MRI) and CSF examinations were evaluated. All patients were screened with computed tomography (CT), MRI, or B-scan ultrasonography at least once for systemic tumors. Each patient's neurological status was assessed using the modified Rankin Scale (mRS) [23]. The neurological scores were defined as follows: 0 = no symptoms; 1 = no significant disability in conducting all usual activities despite some symptoms; 2 = slight disability in conducting personal affairs without assistance but unable to carry out all previous activities; 3 = moderate disability requiring some help but able to walk unassisted; 4 = moderately severe disability, i.e., unable to attend to bodily needs without assistance and unable to walk unassisted; 5 = severe disability requiring constant nursing care and attention as well as being bedridden and incontinent; 6 = dead.

Biochemical Assays

Venous blood samples were collected on admission. Serum C-reactive protein (CRP) and lipid profile levels, including total cholesterol (TC), TG, HDL-C, LDL-C, apoA-I, apoB, and lipoprotein a (LPa), were measured with a Clinical Analyzer 7180-ISE (Hitachi High-Technologies, Tokyo, Japan). The apoB/apoA-I ratios were calculated. CSF herpes simplex virus (HSV) antibodies were detected using a chemiluminescence immunoassay.

Follow-Up Evaluations

Patients were followed up 3 months after admission and received repeated assessments of mRS scores and serum lipid levels in our hospital.

Statistical Analysis

Levels of serum lipids (including TC, TG, HDL-C, LDL-C, apoA-I, apoB, and LPa) and CRP, mRS scores, age, and CSF factors, including CSF white blood cell (WBC) counts, total protein (TP), glucose (Glu), and chloride (CL) are presented as median (range). The Mann-Whitney U test was performed to determine the differences in serum lipids levels between patients with anti-NMDAR encephalitis and CTLs, and between the subgroups of patients with encephalitis. Correlations between serum lipid levels and age, mRS scores, or CSF factors (WBC, TP, Glu, and CL) were analyzed using the Spearman rank correlation test. All statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Demographic and Clinical Features

Table 1 shows the demographic features of the recruited 68 patients with anti-NMDAR encephalitis and the 68 age- and sex-matched CTLs. The median mRS score for patients with anti-NMDAR encephalitis was 4.0 (range 1–5). Of the 68 patients with anti-NMDAR encephalitis,

Table 1. Demographic features of patients with anti-NMDAR encephalitis and healthy controls

	Anti-NMDAR encephalitis patients (n = 68)	Age- and sex-matched CTLs (n = 68)	p value
Age at onset, years	26 (1–64)	26 (1–64)	–
Sex (male:female), n	35:33	35:33	–
mRS	4.0 (1–5)	–	
CSF routine			
CSF WBC, $\times 10^6$	6 (0–197)	–	
CSF TP, g/L	0.27 (0.06–2.85)	–	
CSF Glu, mmol/L	3.37 (0.89–6.23)	–	
CSF CL, mmol/L	123.0 (107.4–137.1)	–	
CSF HSV antibody-positive			
HSV-1 IgM	0	–	
HSV-2 IgM	0	–	
HSV-1/2 IgM	1 (1.5)	–	
HSV-1 IgG	1 (1.5)	–	
HSV-2 IgG	0	–	
HSV-1/2 IgG	2 (2.9)	–	
Tumor comorbidity		–	
Ovarian teratoma	11 (16.2)	–	
Colon carcinoma	1 (1.5)	–	
C-reactive protein, mg/L	2.5 (0.1–99.2)	0.4 (0.0–5.4)	<0.001
Serum lipid levels			
TC, mmol/L	4.21 (2.38–8.91)	4.43 (2.83–6.65)	0.138
TG, mmol/L	1.00 (0.32–7.16)	0.98 (0.38–6.85)	0.776
LDL-C, mmol/L	2.60 (1.07–5.95)	2.41 (1.42–4.34)	0.238
HDL-C, mmol/L	1.08 (0.23-4.00)	1.40 (0.78-2.12)	<0.001
ApoA-I, gmol/L	1.24 (0.36–1.77)	1.35 (0.65–1.94)	0.001
ApoB, gmol/L	0.94 (0.36–1.92)	0.67 (0.41–1.49)	<0.001
ApoB/apoA-I ratio	0.80 (0.32–3.67)	0.48 (0.27–1.10)	<0.001
LPa, mmol/L	133.5 (12.0–1,120)	92.8 (2.1–554.1)	0.063

Values are expressed as n (%) or median (range), unless otherwise indicated. NMDAR, N-methyl-D-aspartate receptor; CTLs, healthy controls; mRS, modified Rankin Scale; CSF, cerebrospinal fluid; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine; ApoA-I, apolipoprotein A-I; apoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LPa, lipoprotein a; HSV, herpes simplex virus.

4 (27.6%) showed CSF HSV antibody positivity, including HSV-1/2 immunoglobulin M (IgM) positivity (n = 1), HSV-1 IgG positivity (n = 1), and HSV-1/2 IgG positivity (n = 2). Twelve patients (17.6%) had complications, including ovarian teratoma (n = 11, 16.2%) and colon carcinoma (n = 1, 1.5%).

Comparison of Serum Lipid Levels in Patients with Anti-NMDAR Encephalitis and CTLs

As shown in Table 1, compared with the CTLs, patients with anti-NMDAR encephalitis had significantly lower serum HDL-C and apoA-I levels but significantly higher CRP and serum apoB levels and apoB/apoA-I ratios. Other serum lipid level differences were not statistically significant.

Comparison of Serum Lipid Levels in the Subgroups of Patients with Anti-NMDAR Encephalitis

As shown in Table 2, when the data were analyzed by age, patients with anti-NMDAR encephalitis aged <18 years had significantly lower serum apoA-I levels and a higher apoB/apoA-I ratio than CTLs aged <18 years. Serum HDL-C and apoA-I levels were significantly lower, whereas serum apoB levels and apoB/apoA-I ratios were significantly higher in patients aged ≥18 years than in CTLs in this age subgroup. The apoB/apoA-I ratio in patients aged <18 was significantly lower than in the patients aged ≥18 years.

Table 3 presents data for patients and CTLs analyzed according to sex. Serum HDL-C and apoA-I levels were significantly lower and serum apoB levels and apoB/

Table 2. Serum lipid levels in different groups analyzed according to age

	Anti-NMDAR encephalitis patients		CTLs		*p*1	*p*2	*p*3	*p*4
	aged <18 years (*n* = 17)	aged ≥18 years (*n* = 51)	aged <18 years (*n* = 17)	aged ≥18 years (*n* = 51)				
TC, mmol/L	4.26 (2.38–5.14)	4.16 (2.62–8.91)	4.27 (3.33–5.83)	4.53 (2.83–6.65)	0.322	0.218	0.346	0.457
TG, mmol/L	0.89 (0.36–1.83)	1.03 (0.32–7.16)	0.74 (0.38–3.89)	0.98 (0.45–6.85)	0.812	0.497	0.135	0.479
LDL-C, mmol/L	2.62 (1.08–3.45)	2.58 (1.07–5.95)	2.28 (1.66–3.43)	2.5 (1.42–4.34)	0.802	0.293	0.483	0.915
HDL-C, mmol/L	1.23 (0.68–2.18)	1.07 (0.23–4.0)	1.40 (0.78–1.99)	1.34 (0.81–2.12)	0.092	<0.001	0.114	0.972
ApoA-I, g/L	1.31 (0.87–1.58)	1.19 (0.36–1.77)	1.41 (0.91–1.86)	1.32 (0.65–1.94)	0.045	0.005	0.147	0.141
ApoB, g/L	0.87 (0.36–1.19)	0.99 (0.46–1.92)	0.71 (0.51–1.25)	0.66 (0.41–1.49)	0.079	<0.001	0.09	0.537
ApoB/apoA-I ratio	0.69 (0.32–0.90)	0.82 (0.34–3.67)	0.48 (0.3–0.91)	0.48 (0.27–1.10)	0.009	<0.001	0.014	0.124
LPa, mmol/L	107.0 (12.0–449.0)	157.0 (15–1120.0)	138.9 (2.1–321.0)	88.5 (30–554.1)	0.433	0.014	0.111	0.848

Values are expressed as median (range). *p*1, patients with anti-NMDAR encephalitis versus controls (CTLs) in the subgroup aged <18 years; *p*2, patients with anti-NMDAR encephalitis versus CTLs in the subgroup aged ≥18 years; *p*3, patients with anti-NMDAR encephalitis aged <18 years vs. patients aged ≥18 years; *p*4, CTLs aged <18 years vs. CTLs aged ≥18 years. For all other abbreviation definitions, see footnote to Table 1.

Table 3. Serum lipid levels in different groups analysed according to sex

	Anti-NMDAR encephalitis patients		CTLs		*p*1	*p*2	*p*3	*p*4
	male (*n* = 35)	female (*n* = 33)	male (*n* = 35)	female (*n* = 33)				
TC, mmol/L	3.9 (2.38–7.97)	4.51 (2.62–8.91)	4.27 (2.83–6.65)	4.64 (3.26–6.01)	0.077	0.526	0.038	0.348
TG, mmol/L	0.97 (0.36–7.16)	1.04 (0.32–2.85)	0.98 (0.38–6.85)	0.97 (0.51–3.89)	0.865	0.617	0.397	0.632
LDL-C, mmol/L	2.49 (1.07–5.73)	2.73 (1.11–5.95)	2.30 (1.42–4.34)	2.55 (1.66–4.22)	0.605	0.284	0.211	0.488
HDL-C, mmol/L	1.03 (0.23–2.44)	1.10 (0.62–4.0)	1.31 (0.78–1.97)	1.40 (1.04–2.12)	0.003	0.001	0.101	0.191
ApoA-I, gmol/L	1.15 (0.36–1.77)	1.29 (0.70–1.64)	1.30 (0.65–1.93)	1.37 (0.81–1.94)	0.015	0.022	0.112	0.105
ApoB, gmol/L	0.87 (0.36–1.92)	0.99 (0.46–1.68)	0.67 (0.46–1.49)	0.66 (0.41–1.25)	<0.001	<0.001	0.531	0.610
ApoB/apoA-I ratio	0.79 (0.32–3.67)	0.80 (0.34–1.74)	0.52 (0.27–1.10)	0.47 (0.3–1.02)	<0.001	<0.001	0.764	0.189
LPa, mmol/L	108.0 (15–1,112.0)	154.0 (12–1,120)	91.4 (30–292.9)	104.6 (2.1–554.1)	0.094	0.485	0.668	0.155

Values are expressed as median (range). *p*1, male anti-NMDAR encephalitis patients vs. male CTLs; *p*2, female anti-NMDAR encephalitis patients vs. female CTL; *p*3, male vs. female anti-NMDAR encephalitis patients; *p*4, male vs. female CTLs. For all other abbreviation definitions, see footnote to Table 1.

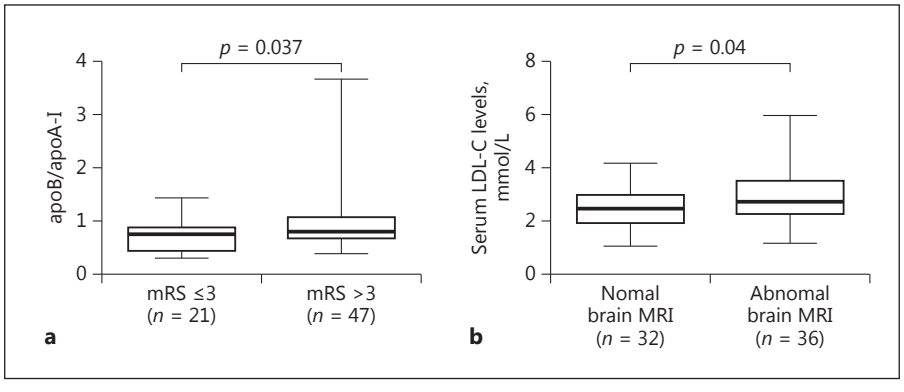

Fig. 1. Serum lipid levels in patients with anti-NMDAR encephalitis according to mRS score and brain MRI. **a** Patients with an mRS score >3 had a significantly higher apoB/apoA-I ratio than those with a score ≤3. **b** Patients with abnormal results on brain MRI had significantly higher LDL-C levels than those with normal results.

apoA-I ratios were significantly higher, in both male and female patients, than in the respective sexes in the CTLs. Serum TC levels were significantly lower in male than in female patients. No other factors differed significantly.

We also divided the patients into subgroups according to their mRS scores and brain MRI results (Fig. 1). Patients with an mRS score >3 had a significantly higher apoB/apoA-I ratio than those with an mRS score ≤3 (*p* =

Table 4. Correlation coefficients generated between serum lipid levels and clinical characteristics, C-reactive protein, or CSF parameters in patients with anti-NMDAR encephalitis

	TC	TG	LDL-C	HDL-C	apoA-I	apoB	apoB/apoA-I	LPa
Age								
r	0.148	0.241	0.176	–0.155	–0.159	0.313	0.349	0.274
p	0.227	0.048	0.150	0.208	0.196	0.009	0.004	0.024
Sex								
r	0.253	0.103	0.153	0.200	0.194	0.076	–0.037	0.052
p	0.037	0.401	0.213	0.102	0.113	0.535	0.766	0.671
mRS								
r	0.027	0.048	0.048	–0.131	–0.157	0.223	0.284	0.067
p	0.828	0.699	0.699	0.285	0.202	0.068	0.019	0.590
CRP								
r	0.038	0.321	0.026	–0.279	–0.282	0.309	0.370	0.075
p	0.760	0.008	0.834	0.021	0.02	0.010	0.002	0.542
CSF WBC								
r	0.246	–0.049	0.337	–0.069	–0.042	0.232	0.149	0.022
p	0.043	0.694	0.005	0.575	0.736	0.057	0.224	0.861
CSF TP								
r	–0.194	0.011	–0.117	–0.176	–0.143	–0.056	–0.003	0.169
p	0.113	0.929	0.343	0.151	0.246	0.653	0.979	0.169
CSF Glu								
r	0.141	–0.027	0.046	0.170	0.139	0.126	0.008	–0.122
p	0.252	0.830	0.708	0.165	0.259	0.304	0.950	0.321
CSF CL								
r	0.071	0.273	–0.031	–0.013	–0.014	0.069	0.087	–0.038
p	0.567	0.054	0.801	0.919	0.908	0.576	0.482	0.759

Anti-NMDAR, anti-N-methyl-D-aspartate receptor; mRS, modified Rankin Scale; CSF, cerebrospinal fluid; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chloride; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; LPa, lipoprotein a; CRP, C-reactive protein.

0.037; Fig. 1a). Patients with abnormal brain MRI results had significantly higher LDL-C levels than those with normal brain MRI results ($p = 0.04$; Fig. 1b). No other serum lipids differed significantly.

Association between Serum Lipid and CRP Levels, Clinical Characteristics, or CSF Parameters in Patients with Anti-NMDAR Encephalitis

The relationships between serum lipid levels and clinical characteristics or CSF parameters in patients with anti-NMDAR encephalitis were evaluated and the results are presented in Table 4. Serum TG, apoB, and LPa levels as well as the apoB/apoA-I ratio were significantly and positively correlated with age. Serum TC levels were significantly and positively associated with sex. Serum CRP levels were significantly and negatively associated with serum HDL-C and apoA-I levels but significantly and positively associated with serum TG and apoB levels. The apoB/apoA-I ratio was significantly and positively correlated with the mRS score. Serum TC and LDL-C levels were significantly correlated with the CSF WBC counts. However, correlations between serum lipid levels and CSF TP, Glu, and CL levels were not significant.

Follow-Up Evaluation after Treatment Examining Serum Levels in Patients with Anti-NMDAR Encephalitis

Of the 68 patients with anti-NMDAR encephalitis, 32 had a follow-up evaluation 3 months after admission; their serum lipid levels and mRS scores are shown in Figure 2. Following anti-NMDAR encephalitis treatment, serum TC, HDL-C, and apoA-I levels were significantly increased (Fig. 2a–c), whereas mRS scores were significantly decreased (Fig. 2d). No other serum lipid levels differed significantly. However, the changes in the mRS

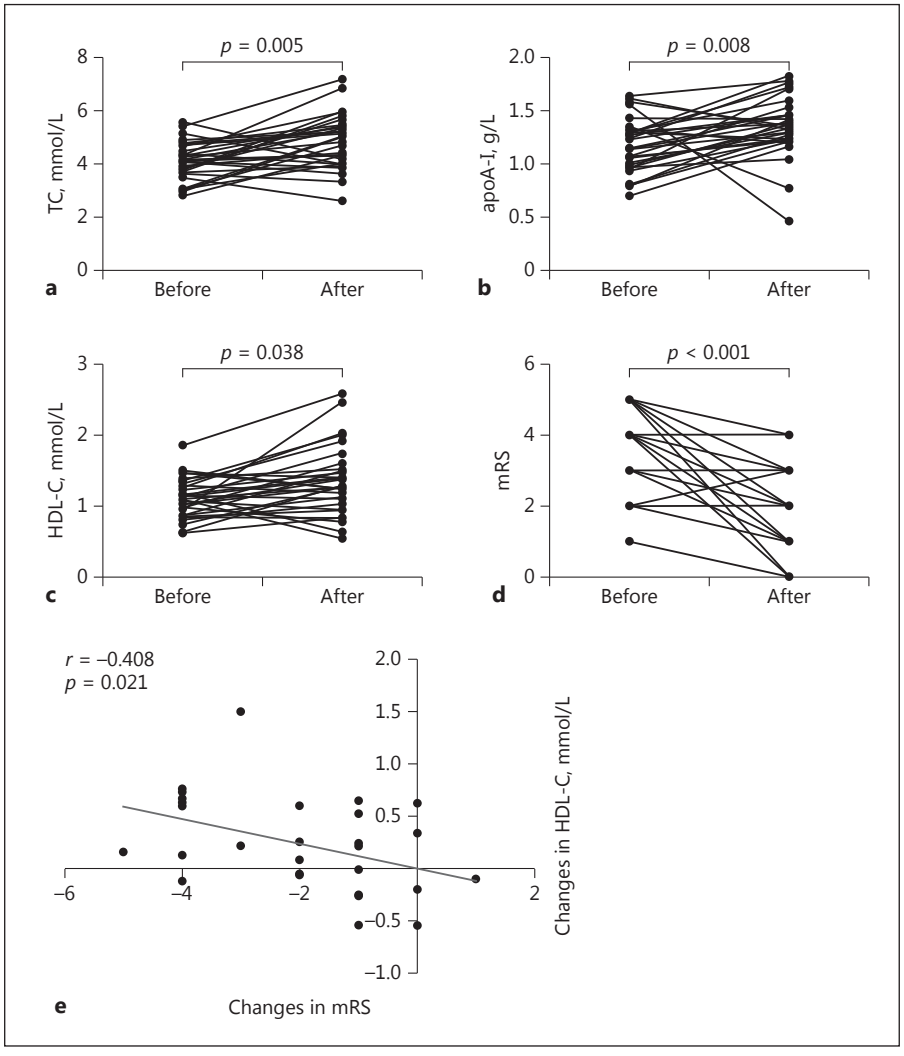

Fig. 2. a–d Changes between initial admission and follow-up after treatment in serum TC, apoA-I, and HDL-C levels, and mRS scores in patients with anti-NMDAR encephalitis. **e** Changes in mRS scores are significantly and negatively correlated with HDL-C level changes.

scores were significantly and negatively associated only with the changes in the HDL-C levels ($r = -0.408$, $p = 0.021$; Fig. 2e).

Discussion

This observational study showed that serum HDL-C levels in patients during the initial phase of anti-NMDAR encephalitis were significantly lower than in CTLs, and this was especially evident in the subgroup aged ≥18 years. In the follow-up evaluation after 3 months of treatment, significantly increased levels of serum TC, HDL-C, and apoA-I were found, but only increased serum HDL-C levels were significantly and negatively associated with decreased mRS scores. To the best of our knowledge, this study is the first to analyze serum cholesterol and lipoprotein levels in patients with anti-NMDAR encephalitis.

The potential mechanisms whereby serum lipids may underpin anti-NMDAR encephalitis remain unclear. However, lipid metabolism has been demonstrated to be involved in other inflammatory and autoimmune disorders [8–13]. For example, LDL has been found to be taken up by activated microglia and infiltrating macrophages in MS plaques and play an important role in MS pathogenesis [12], while HDL potentially inhibits the initiation and maintenance of pathogenic BBB injury in MS [11]. The main component of HDL, apoA-I, has been implicated in several functions, including protecting against oxidative stress [24], the inflammatory response [13], and amyloid beta-induced neurotoxicity [25]. Low levels of HDL-C have been described in patients with severe sepsis

[26], severe meningococcal sepsis [27], and nosocomial infections [28]. In this study, we also found that serum HDL-C and apoA-I levels were significantly reduced in the initial phase of anti-NMDAR encephalitis. We speculate that low levels of serum HDL-C and apoA-I in the initial phase may impair the innate immune response against inflammation and heighten susceptibility to an overactive inflammatory response, facilitating an anti-NMDAR encephalitis attack. Further study on the potential mechanism of serum lipids in anti-NMDAR encephalitis will be required.

It is impossible to ascertain whether low levels of serum HDL-C and apoA-I are a cause or a consequence of the anti-NMDAR encephalitis-related inflammatory response. In this study, serum HDL-C and apoA-I levels were reduced in the initial phase of anti-NMDAR encephalitis and were negatively associated with serum CRP. Therefore, low serum HDL-C and apoA-I levels may be responsible for the initial phase inflammatory response in this disease. Because apolipoproteins are synthesized in the liver, some inflammatory cytokines may decrease the hepatic synthesis or secretion of apolipoproteins [29]; this may partly explain the low HDL-C and apoA-I levels observed in anti-NMDAR encephalitis. However, further studies investigating the association between low serum lipid levels and anti-NMDAR encephalitis will be required.

In this study, serum apoB levels were significantly higher and positively correlated with CRP in patients with anti-NMDAR encephalitis. Increasing evidence indicates that serum apoB is the primary predictor of inflammatory markers [14, 20]. Therefore, the high levels of apoB observed here reflected the strong inflammatory response in the initial phase of anti-NMDAR encephalitis. Furthermore, serum apoB was significantly and positively associated with age in these patients. We found that serum apoB levels appeared to be higher in patients who were ≥18 years old than in younger patients, although this trend was not statistically significant ($p = 0.09$). We speculate that older patients may suffer from more powerful inflammatory stress, and that the statins that effectively modulate serum lipid metabolism may be beneficial in the treatment of anti-NMDAR encephalitis. In addition, the older patients had a higher apoB/apoA-I ratio. This ratio was significantly and positively associated with age, CRP, and mRS score, suggesting that it may also be an inflammatory marker for anti-NMDAR encephalitis. Additional extensive epidemiological studies will be required to test this.

The low levels of TC, HDL-C, and apoA-I observed in the initial phase of anti-NMDAR encephalitis were significantly increased after 3 months of treatment. The mechanisms underlying the recovery of TC, HDL-C, and apoA-I levels are unknown. Serum cholesterol and apolipoprotein levels may be influenced by many factors, including disease severity, diet, and treatment. One plausible explanation for the increase in serum cholesterol and lipoprotein levels may be associated with the reduced inflammatory response and oxidative stress observed in patients with anti-NMDAR encephalitis after treatment. Higher serum HDL-C has been associated with lower levels of BBB injury and decreased CD80+ and CD80+CD19+ cell extravasation into the CSF in MS [11]. Another plausible explanation is that patients were able to assimilate sufficient nutrients once they had been treated and were recovering. Finally, all patients with follow-up were treated with steroids, which might also have affected their lipid metabolism. Therefore, clarifying the underlying mechanisms will require further studies.

We acknowledge that there were some limitations in our study. First, the sample size was small ($n = 68$), suggesting that our results may not accurately represent anti-NMDAR encephalitis. Second, this study referred to an inflammatory response in anti-NMDAR encephalitis. However, only serum CRP (an inflammatory marker) was evaluated, but other markers, such as IL-6 and TNF-α, were not examined. Third, we tested for CSF HSV-1/2 antibody positivity in patients to assess whether anti-NMDAR encephalitis followed a viral CNS infection. However, the detection of CSF HSV-1/2 should be conducted by using real-time PCR technology [5]. Fourth, the method for the detection of anti-NMDAR antibodies was not quantitative, so the relation between the levels of the antibodies and the serum lipids was not determined. This remains an area for future study.

Conclusion

Our results showed that patients in the initial phase of anti-NMDAR encephalitis had low HDL-C and apoA-I levels but high apoB levels and apoB/apoA-I ratios. Serum TC, HDL-C, and apoA-I levels recovered after treatment. The increased levels of serum HDL-C were associated with decreased disease severity. Further studies on the role of serum lipids in anti-NMDAR encephalitis are required.

Acknowledgements

This study was supported by a grant from the National Natural Science Foundation of China (81701188).

Statement of Ethics

This study conformed to the code of ethics of the World Medical Association (the Declaration of Helsinki), and was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University. Informed written consent was obtained from the patients or their representatives.

Disclosure Statement

The authors declare that they have no competing interests.

References

1 Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–1098.

2 Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66:11–18.

3 Vincent A, Bien CG: Anti-NMDA-receptor encephalitis: a cause of psychiatric, seizure, and movement disorders in young adults. Lancet Neurol 2008;7:1074–1075.

4 Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J: Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011;77: 589–593.

5 Armangue T, Leypoldt F, Malaga I, Raspall-Chaure M, Marti I, Nichter C, Pugh J, Vicente-Rasoamalala M, Lafuente-Hidalgo M, Macaya A, Ke M, Titulaer MJ, Hoftberger R, Sheriff H, Glaser C, Dalmau J: Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2014;75:317–323.

6 Venkatesan A, Benavides DR: Autoimmune encephalitis and its relation to infection. Curr Neurol Neurosci Rep 2015;15:3.

7 Linnoila JJ, Binnicker MJ, Majed M, Klein CJ, McKeon A: CSF herpes virus and autoantibody profiles in the evaluation of encephalitis. Neurol Neuroimmunol Neuroinflamm 2016; 3:e245.

8 Reale M, Sanchez-Ramon S: Lipids at the cross-road of autoimmunity in multiple sclerosis. Curr Med Chem 2017;24:176–192.

9 Alipour A, van Oostrom AJ, Izraeljan A, Verseyden C, Collins JM, Frayn KN, Plokker TW, Elte JW, Castro CM: Leukocyte activation by triglyceride-rich lipoproteins. Arterioscler Thromb Vasc Biol 2008;28:792–797.

10 Hoover-Plow J, Hart E, Gong Y, Shchurin A, Schneeman T: A physiological function for apolipoprotein(A): a natural regulator of the inflammatory response. Exp Biol Med (Maywood) 2009;234:28–34.

11 Fellows K, Uher T, Browne RW, Weinstock-Guttman B, Horakova D, Posova H, Vaneckova M, Seidl Z, Krasensky J, Tyblova M, Havrdova E, Zivadinov R, Ramanathan M: Protective associations of HDL with blood-brain barrier injury in multiple sclerosis patients. J Lipid Res 2015;56:2010–2018.

12 Newcombe J, Li H, Cuzner ML: Low density lipoprotein uptake by macrophages in multiple sclerosis plaques: implications for pathogenesis. Neuropathol Appl Neurobiol 1994; 20:152–162.

13 Burger D, Dayer JM: High-density lipoprotein-associated apolipoprotein A-I: the missing link between infection and chronic inflammation? Autoimmun Rev 2002;1:111–117.

14 Faraj M, Messier L, Bastard JP, Tardif A, Godbout A, Prud'Homme D, Rabasa-Lhoret R: Apolipoprotein B: a predictor of inflammatory status in postmenopausal overweight and obese women. Diabetologia 2006;49: 1637–1646.

15 Uher T, Fellows K, Horakova D, Zivadinov R, Vaneckova M, Sobisek L, Tyblova M, Seidl Z, Krasensky J, Bergsland N, Weinstock-Guttman B, Havrdova E, Ramanathan M: Serum lipid profile changes predict neurodegeneration in interferon-β1a-treated multiple sclerosis patients. J Lipid Res 2017;58:403–411.

16 Villoslada P, Alonso C, Agirrezabal I, Kotelnikova E, Zubizarreta I, Pulido-Valdeolivas I, Saiz A, Comabella M, Montalban X, Villar L, Alvarez-Cermeno JC, Fernandez O, Alvarez-Lafuente R, Arroyo R, Castro A: Metabolomic signatures associated with disease severity in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2017;4:e321.

17 Li Y, Wang H, Hu X, Peng F, Yang Y: Serum lipoprotein levels in patients with neuromyelitis optica elevated but had little correlation with clinical presentations. Clin Neurol Neurosurg 2010;112:478–481.

18 Zhong YH, Liu J, Li M, Wang X, Yuan Y, Zhong XF, Peng FH: Distinct serum apolipoprotein A-I levels in neuromyelitis optica and acute transverse myelitis. Lipids Health Dis 2013;12:150.

19 Borba EF, Carvalho JF, Bonfá E: Mechanisms of dyslipoproteinemias in systemic lupus erythematosus. Clin Dev Immunol 2006;13:203–208.

20 Onat A, Can G, Hergenc G, Yazici M, Karabulut A, Albayrak S: Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation. Int J Obes (Lond) 2007;31: 1119–1125.

21 Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Hoftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Pruss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostasy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J: A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391–404.

22 Shu Y, Wang Y, Lu T, Li R, Sun X, Li J, Chang Y, Hu X, Lu Z, Qiu W: Serum uric acid and anti-N-methyl-D-aspartate receptor encephalitis. Neurochem Int 2017;108:34–39.

23 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.

24 Rosenson RS: Beyond low-density lipoprotein cholesterol. A perspective on low high-density lipoprotein disorders and Lp(a) lipoprotein excess. Arch Intern Med 1996;156: 1278–1284.

25 Paula-Lima AC, Tricerri MA, Brito-Moreira J, Bomfim TR, Oliveira FF, Magdesian MH, Grinberg LT, Panizzutti R, Ferreira ST: Human apolipoprotein A-I binds amyloid-beta and prevents Abeta-induced neurotoxicity. Int J Biochem Cell Biol 2009;41:1361–1370.

26 van Leeuwen HJ, Heezius EC, Dallinga GM, van Strijp JA, Verhoef J, van Kessel KP: Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003;31:1359–1366.

27 Vermont CL, den Brinker M, Kakeci N, de Kleijn ED, de Rijke YB, Joosten KF, de Groot R, Hazelzet JA: Serum lipids and disease severity in children with severe meningococcal sepsis. Crit Care Med 2005;33:1610–1615.

28 Delgado-Rodriguez M, Medina-Cuadros M, Martinez-Gallego G, Sillero-Arenas M: Total cholesterol, HDL-cholesterol, and risk of nosocomial infection: a prospective study in surgical patients. Infect Control Hosp Epidemiol 1997;18:9–18.

29 Ettinger WH, Varma VK, Sorci-Thomas M, Parks JS, Sigmon RC, Smith TK, Verdery RB: Cytokines decrease apolipoprotein accumulation in medium from Hep G2 cells. Arterioscler Thromb 1994;14:8–13.