Association between carotid plaque and Parkinson's disease

Lan-Yun Yan[1#], Qing-Fang He[2#], Min-Yan Lu[2#], Sheng-Long Wang[2], Zhi-Qiang Qi[2], Hai-Rong Dong[1,2]

[1]Department of Neurology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China; [2]Department of Neurology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, Suzhou 215228, China

Contributions: (I) Conception and design: HR Dong, ZQ Qi, SL Wang; (II) Administrative support: HR Dong, ZQ Qi; (III) Provision of study materials or patients: ZQ Qi, SL Wang; (IV) Collection and assembly of data: LY Yan, QF He, MY Lu; (V) Data analysis and interpretation: LY Yan, ZQ Qi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dr. Hai-Rong Dong. Department of Neurology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, No.1399 Shichang West Road, Shengze Town, Wujiang District, Suzhou 215228, China. Email: 13814095902@163.com; Dr. Zhi-Qiang Qi. Department of Neurology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, No. 1399 Shichang West Road, Shengze Town, Wujiang District, Suzhou 215228, China. Email: qzqhp@sina.com; Dr. Sheng-Long Wang. Department of Neurology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, No. 1399 Shichang West Road, Shengze Town, Wujiang District, Suzhou 215228, China. Email: 2837012866@qq.com.

Background: Epidemiological studies show that patients with Parkinson's disease (PD) are prone to have a reduced incidence of ischemic cerebrovascular disease. Previous studies show the correlation between PD and the lipids serum levels. The PD,s patients are found with a reduced serum level of triglyceride and low-density lipoprotein cholesterol (LDL-C); thus, the level of serum uric acid (UA) is closely related to the occurrence and development of PD. Patients with low serum UA levels have a higher chance of developing PD than the ones who do not. However, the relationship between carotid plaques and PD is still unknown.

Methods: Our study was based on 68 patients with PD (known as the PD group) and 81 people without PD (known as the control group). Patients in the PD group were of the same age and gender. Both groups were recorded and analyzed for UA, LDL-C, and carotid plaques or intima-media thickness (IMT). The PD group was then divided into three subgroups: the stable plaque group, the unstable plaque group, and the non-plaque group.

Results: In the present study, the PD group showed a significantly lower level of UA and LDL-C than the control group ($P<0.01$); somehow there were no statistically significant differences in the IMT and plaque incidence between the two groups ($P>0.05$). There were also no significant differences ($P>0.05$) in both the LDL-C and UA levels in all subgroups, but there was a close relation in both age and duration of disease to IMT. According to the Hoehn and Yahr staging scale, serum levels of LDL-C were inversely correlated in PD patients, while UA was related to the duration of the disease.

Conclusions: Our study suggested that there were no differences in carotid artery arteriosclerosis plaque and IMT, but the PD progress was indeed correlated with IMT. Meanwhile, LDL-C and UA had different priorities in H&Y and disease progression.

Keywords: Carotid plaque; risk factors; Parkinson's disease (PD)

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders that classically presents with extrapyramidal symptoms and nonmotor symptoms (1). The disease manifests as a resting tremor, with rigidity, bradykinesia, and postural instability, and it can also be accompanied by several other nonmotor symptoms such as muscular pain, anxiety, depression and other disturbances (2). The mutations of some known genes lead to some PD cases; however, this disorder is mostly the result of an interaction with the inherent genetic and environmental effect conditions (3). Both genetic and environmental factors conduce to the pathogenetic process of PD (1). It is characterized by a diminishing of dopaminergic neurons located in the substantia nigra. Several biological processes mechanisms for the degeneration of nigrostriatal neurons are oxidative stress (4), inflammation (5), mitochondrial dysfunction (6) and protein aggregation (7), with oxidative stress and mitochondrial dysfunction being considered as playing the most significant roles. Urate is a robust endogenous antioxidant, serum uric acid (UA), in particular, has recently drawn extensive clinical attention. There are plenty of studies which have revealed that high levels of serum or plasma urate reduced the risk of PD (8-10). Ascherio et al. showed that he higher serum and cerebrospinal fluid urate concentrations at baseline could be slowed down in the progression of PD, implying a potential neuroprotection with a high level of urate in PD patients (11). Meanwhile, another study found that the elevation of serum UA was associated with the occurrence and development of PD. The patients with a low level of serum UA may easily develop PD (12). Moreover, other research (13-15) has also suggested the effect of lipid and cholesterol metabolism in the pathogenesis of PD. Serum cholesterol is a crucial, decisive factor of serum coenzyme Q10 levels, while coenzyme Q10 works as a powerful mitochondrial electron and antioxidant acceptor, and can lead to beneficial effects in PD patients (16).

Hyperlipidemia and hyperuricemia are independent risk factors for cardiovascular disease. The Kumral study (17) found that a higher level of UA and carotid artery disease (CAD) are closely interrelated. Lectin-like oxidized low-density lipoprotein 1(LOX1) may be one of the non-neglected factors during the formation of vulnerable carotid plaque (18). Struck et al. (19), and other professors (20) have reported that, in PD patients, the UA and LDL-C were significantly lower in the PD group than those in healthy, people and the risk of stroke decreased. Also, one study by Korten et al. found that among 1,516 stroke patients, there were only eight PD individuals (21). However, up to now, the study of the carotid plaque of PD patients still has not been clarified. Therefore, a retrospective study focussing on the carotid plaque of PD patients and the relationship between plaque with UA and LDL-C was carried out.

Methods

A total of 68 patients who were diagnosed by the UK PD Society Brain Bank criteria (22) in Jiangsu Sheng hospital between January 2010 and October 2017. We excluded patients with Parkinsonism syndrome, Parkinsonism plus syndrome, severe heart and cerebrovascular disease, and liver and kidney disease. Meanwhile, the control group consisted of 81 healthy people, who were at the same age period and gender as the participants in the PD group. The study was approved by the Ethics Committee of the Nanjing Medical University (JSSZYYLL-20181126-01), and written informed consent was obtained from all the participants.

The 5-mL fasting blood of the ulnar vein was taken from all subjects who had stopped their high-fat and high-purine diet a day before. The content of UA and LDL-C were determined by the Roche P800 fully automatic biochemical analyzer. Each PD patient was evaluated according to the following H&Y stages: (I) unilateral involvement usually only with minimal or no functional disability; (II) bilateral or midline involvement without impairment of balance; (III) bilateral disease of mild to moderate disability with impaired postural reflexes but physically independent; (IV) Severely disabling disease with the ability to still walk or stand unassisted; (V) confinement to bed or wheelchair unless otherwise aided.

Using ultrasound, the vascular morphologic changes, endothelial function, and the echo of plaques were measured in the common carotid artery (CCA), the bifurcation of CCA, and the proximal segment of the unilateral internal carotid artery (ICA). The built-in software of the ultrasound system was used to calculate the total intima-media surface of this selected area online. The definition of carotid plaques is thickened walls of local blood vessels, and consists of any one of the following criteria: the intima-media thickness (IMT) being ≥1.3 mm, the limitations bulge protruding into the lumen ≥2.5 mm, or the IMT thickened more than 50% of the surrounding tissue (23). We define

Table 1 The demographic characteristics of two groups

Demographic factors and history	PD (N)	Control (N)	P
Male	38	44	>0.05
Female	30	37	>0.05
Age (years)[a]	72.41±9.27	71.60±9.70	>0.05
Disease duration (years)[b]	3.26±2.58	/	/
Hypertension	18	28	>0.05
Diabetes mellitus	0	0	/
Smoke	15	18	>0.05
Alcohol	15	17	>0.05

Means (standard deviations) are provided for continuous variables and numbers (proportions) are provided for categorical variables. [a], ages of cases and controls were based at time of fasting lipid profile testing; [b], disease durations were calculated based at time of fasting lipid profile testing from the date of PD diagnosis. PD, Parkinson's disease.

Table 2 Comparison of LDL-C, UA levels, carotid plaques and IMT in Parkinson's disease group and control group

Groups	PD (n=68)	Control (n=81)	T or X^2	P
LDL-C (mmol/L)	2.57±0.98	2.96±0.75	−2.70	0.008**
UA (μmol/L)	282.38±92.81	331.07±96.51	−3.12	0.002**
Plaque (n)	33	46	1.013	0.314
IMT (cm)	0.95±0.29	0.95±0.22	0.049	0.961

Compared with the control group, **, $P<0.01$. LDL-C, low-density lipoprotein cholesterol; UA, uric acid; IMT, intima-media thickness.

the uniformly, predominantly and mixed echo lucent as the unstable plaques, while the predominantly and uniformly echogenic plaques as the stable plaques.

All the statistical analyses were performed with the SPSS 22.0 for Windows. The measurement data were presented as mean ± SD, while the *t*-test was used to compare the two independent sample means, and the chi-square test was used for the comparison of enumeration data. The differences of mean among the three groups were determined with one-way analysis of variance. The Pearson and Spearman correlation analysis were used to test the differences in IMT between groups holding consistent age courses of the disease and the illness severity. The statistical significance was set at $P \leq 0.05$ level.

Results

Table 1 shows the demographics, the history of hypertension, smoking status, diabetes and the use of alcohol in both groups. There were no significant differences between the two groups in gender, age, history of hypertension, diabetes mellitus and the use of alcohol.

Among the total of 68 patients in the PD group, there were 38 males and 30 females, aged 39–86 (72.41±9.27) years. The time of disease was 0.1–10 (3.26±2.58) years. The PD group had the following H&Y stage distribution: 33 cases were stage 1 to 2, 26 cases were stage 2.5 to 3, and 9 cases were above 3 stage. Forty-four males and 37 females were in the control group, and the mean age was 71.60±9.70 years.

As shown in *Tables 2,3*, in the PD group, the serum UA level was 282.38±92.81 μmol/L, while in the control group the serum UA level was 331.07±96.51 μmol/L. There was a significant difference in serum levels of UA for the two groups (P=0.002). PD patients had a significantly lower serum UA level than the control subjects. In the PD group, the serum LDL-C level was 2.57±0.98 mmol/L, while in the control group the serum LDL-C level was

Table 3 The comparison between LDL-C and UA levels in the non-plaque group, stable plaque group, and unstable plaque group of Parkinson's patients

Risk factors	Non-plaque group	Stable plaque group	Unstable plaque group	F	P
LDL-C (mmol/L)	2.54±0.94	2.45±0.58	2.74±1.28	0.38	0.69
UA (μmol/L)	293.14±80.53	251.64±131.01	284.78±80.27	1.02	0.37

LDL-C, low-density lipoprotein cholesterol; UA, uric acid.
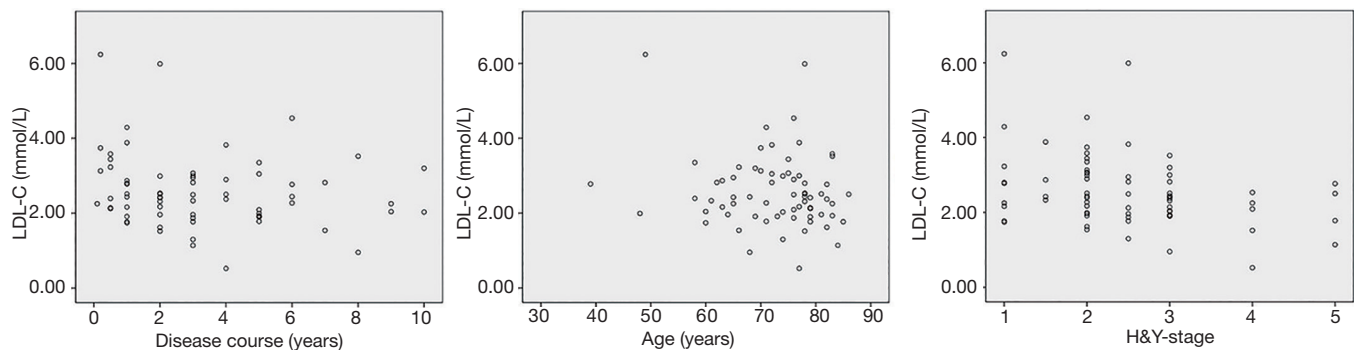
Figure 1 Scatter plot of LDL-C with disease duration, age and H&Y in patients with Parkinson's disease. LDL-C has a significant correlation with H&Y (P<0.01), but not with disease duration and age. LDL-C, low-density lipoprotein cholesterol.

2.96±0.75 mmol/L. There was a significant difference in serum levels of LDL-C for the two groups (P=0.008). PD patients had a significantly lower serum LDL-C level than the control subjects. However, 33 of PD patients were detected the carotid plaques, and 46 subjects in the control group had carotid plaques. Neither the mean of the IMT of the CCA nor the incidence of carotid plaque demonstrated any difference in the two groups. As for three subgroups of the Parkinson's patients, we observed the level of LDL-C and UA. We found that there were no significant differences among these subgroups.

Pearson correlation analysis showed a significant correlation between LDL-C and H&Y (P=0.006<0.01), and there was a strong association between UA and disease duration (P=0.023<0.05) (*Figures 1,2* and *Table 4*). IMT was associated with age, disease course, and severity of the disease (*Figure 3* and *Table 5*). Multiple linear regression analysis predicting the relationship among variables showed that IMT had a significant association with age and disease duration (*Tables 6-8*).

Discussion

This study shows that UA and LDL-C in Parkinson's patients were significantly lower than in the control group.

However, there was no significant difference between carotid IMT and plaque incidence rate. Patients with PD were divided into three subgroups, and the results showed that there were no significant differences among the three groups. Pearson correlation analysis showed a significant correlation among IMT and age, duration of disease and H&Y stage.

We found significantly lower LDL-C in cases that developed PD, compared with controls. These results were consistent with previous studies. For example, one study suggested that a high level of total cholesterol increased the risk of PD (24). The study by Scigliano *et al.* found that the level of TG was significantly lower in PD patients than in control patients who had other non-cerebrovascular neurological diseases (14). A retrospective study found that the serum levels of TG, VLDL-C, and apoB were significantly lower in the PD group than in any other groups with non-cerebrovascular neurological diseases, acute intracerebral hemorrhage and acute cerebral infarction (25). Many environmental risk factor studies corroborated the involvement of insufficient lipid and lipoprotein in the pathophysiology of PD. As described above, high levels of plasma total cholesterol are related to a lower risk of PD.

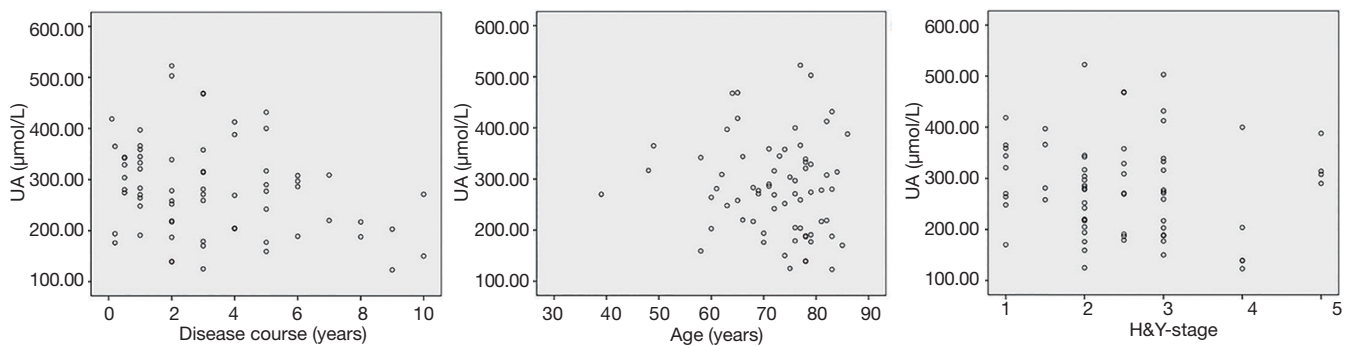Nevertheless, contrary results were also found. Vikdahl (26)

Figure 2 Scatter plot of UA with disease duration, age and H&Y in patients with Parkinson's disease. The level of UA has a significant correlation with disease duration (P<0.05), but not with age and H&Y. UA, uric acid.

Table 4 Correlations analysis of LDL-C and UA with age, disease duration, and severity of disease in patients with Parkinson's disease

Relevant factors	LDL-C (mmol/L)		UA (μmol/L)	
	R value	P value	R value	P value
Disease duration	−0.186	0.128	−0.275	0.023*
Age	−0.155	0.206	−0.102	0.41
H&Y stage	−0.329	0.006**	−0.076	0.538

Compared with the control group, *, P<0.05. LDL-C, low-density lipoprotein cholesterol; UA, uric acid.
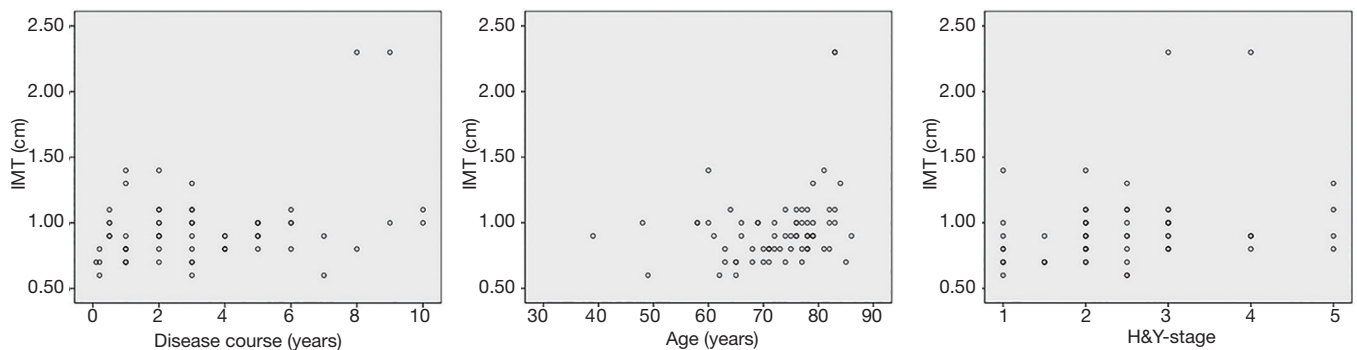

Figure 3 Scatter plot of IMT with disease course, age and H&Y in patients with Parkinson's disease. IMT has a significant correlation with disease duration, age and H&Y (P<0.05). IMT, intima-media thickness.

Table 5 Correlations analysis of carotid intima-media thickness with age, disease duration, and severity of disease in patients with Parkinson's disease

Relevant factors	IMT (cm)	
	R	P
Disease duration	0.351	0.003**
Age	0.276	0.023*
H&Y	0.339	0.005**

Compared with the control group, *, P<0.05; **, P<0.01.

found that there were no differences in serum cholesterol levels between cases and controls. Higher intake of polyunsaturated fatty acid might be inversely associated with PD risk (27). Other studies showed that low levels of plasma LDL were associated with increased PD risk (13,28), whereas high levels of plasma HDL and CSF oxysterol were linked to a higher PD risk and duration (29,30). Finally, in PD patients, high levels of sphingolipids, oxysterols, and oxidized LDL were found in the plasma (31,32).

Given an aging society, more and more carotid plaque is

Table 6 Model summary[c]

Model	R	R square	Adjusted R square	Std. error of the estimate	R square change	F change	df1	df2	Sig. F change
1	0.549[a]	0.301	0.267	0.33646	0.301	8.722	3	60	0.000
2	0.547[b]	0.299	0.276	0.33429	−0.002	0.205	1	60	0.652

[a], predictors: (constant), age, disease duration, H&Y; [b], predictors: (constant), age, disease duration; [c], dependent variable: IMT. IMT, intima-media thickness.

Table 7 Anova[c]

No.	Model	Sum of squares	df	Mean square	F	Sig.
1	Regression	2.962	3	0.987	8.722	0.000[a]
	Residual	6.872	61	0.113		
	Total	9.834	64			
2	Regression	2.939	2	1.469	13.150	0.000[b]
	Residual	6.895	62	0.112		
	Total	9.834	64			

[a], predictors: (constant), age, disease duration, H&Y; [b], predictors: (constant), age, disease duration; [c], dependent variable: IMT. IMT, intima-media thickness.

Table 8 The coefficients a of multiple linear regression analysis[a]

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.	Correlation		Collinearity statistics	
	B	Std. error	beta			Partial	Part	Tolerance	VIF
1 (constant)	−0.085	0.345		−0.246	0.806				
Age	0.013	0.005	0.309	2.468	0.016	0.302	0.265	0.733	1.364
Disease duration	0.066	0.017	0.461	3.773	0.000	0.436	0.405	0.772	1.295
H&Y stage	−0.024	0.054	−0.063	−0.453	0.652	−0.058	−0.049	0.586	1.705
2 (constant)	−0.046	0.332		−0.137	0.891				
Age	0.012	0.005	0.281	2.612	0.011	0.315	0.278	0.984	1.016
Disease duration	0.062	0.015	0.435	4.047	0.000	0.458	0.431	0.984	1.016

[a], dependent variable: IMT. IMT, intima-media thickness.

found with the increasing use of statins, and it is important to determine whether long-term statin usage may also lead to a higher PD risk by lowering plasma cholesterol levels. Huang *et al.* reported that statin use could increase the risk of PD, and higher levels of plasma total or LDL cholesterol were associated with a lower risk of PD (33). It is well-established that serum cholesterol is closely related to coenzyme Q10, which itself acts as a potent endogenous antioxidant, and, as a vital electron acceptor, plays a role in the mitochondrial respiratory chain. Coenzyme Q10 and cholesterol are derived from the same biosynthetic pathway; in fact, all of the coenzyme Q10 in plasma is incorporated in lipoproteins, primarily the LDL-C (34), and thus, coenzyme Q10 could be a possible therapy for PD.

In this study, the levels of serum UA in PD were significantly lower than those in control subjects (*Table 2*), and this result was consistent with previous findings (35,36) showing that lower UA levels may lead to exacerbating

PD as a result of oxidative stress in PD (37). The inverse relationship between UA and severity of PD is different for males and females (12). Whether *in vivo* or *in vitro* in PD models, the protective effect on nigral dopaminergic neurons has been confirmed (38,39).

Higher UA level is demonstrated to be strongly associated with CAD. The higher UA level is significantly associated with the pathological changes in the carotid artery. In addition, IMT of the bifurcation to hyperuricemia which indicates the higher UA level as an accelerating agent, acts on the process of carotid atherosclerosis (17). It is also known that high plasma levels of lipids and lipoproteins are associated with stroke (40). LDL-C was independently associated with atherosclerosis presence and extent (41). Some studies have found that long-term application of levodopa in the treatment of PD can cause plasma Hcy to increase (42). Elevated plasma Hcy may lead to carotid artery thickening and be involved in carotid plaque formation (43).

However, in our study, there were no differences in IMT and plaque between the PD group and the control group. Even in the subgroups, there was no significant difference in the level of LDL-L and UA. These results indicated that some other factors take part in the process of atherosclerosis. Therefore, we analyzed the correlation between the LDL-C, UA, age, duration of disease and H&Y. There was a significant correlation between LDL-C and the H&Y, while UA was related to the length of disease. IMT correlated with age, duration of disease and H&Y, so we performed multiple linear regression analysis and found that age and duration of disease were strictly related to IMT. Serum levels of LDL-C were inversely correlated with H&Y in PD patients, while UA was related to disease progression. In PD patients, like other diseases, age contributes to the process of IMT; at the same time, disease progress also plays a role in the carotid artery arteriosclerosis, although we do not know the exact mechanism.

In conclusion, we found that there were no differences in carotid artery arteriosclerosis plaque and IMT, but the PD progress indeed was correlated with IMT. LDL-C and UA, to some extent, have different priorities with H&Y and disease progression. As for the exact mechanism, unfortunately, we did not have specific and accurate answers.

Using only cross-sectional studies, and small sample sizes is a deficiency in our study. Further prospective studies are needed to confirm the results. Because of these deficiencies, our research only could reach preliminary conclusions.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethics Committee of the Nanjing Medical University (JSSZYYLL-20181126-01), and written informed consent was obtained from all the participants.

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