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Research Article

Involvement of Autonomic Nervous System and its Relationship With Cranial and Cervical Spinal MRI Findings In Patients With Multiple Sclerosis

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Summary

Background and Purpose: Multiple Sclerosis (MS) can be accompanied by autonomic dysfunction which has an important impact on the disability. The aim of this study was to compare the frequency of autonomic abnormalities in MS patients and controls using standard autonomic tests and heart rate variability. It was also aimed to seek any relationship between cranial and cervical spinal magnetic resonance imaging (MRI) findings with autonomic tests and heart rate variability.
Methods: Twenty-four (68.6%) relapsing-remitting, eleven (31.4%) secondary progressive MS patients and 21 age matched controls were enrolled in the study. All subjects underwent standard autonomic function tests assessing parasympathetic (heart rate responses to Valsalva maneuver, deep breathing, and active change of posture) and sympathetic function (blood pressure responses to active change of posture) as well as heart rate variability analysis both for a 24-hour period and during tilt testing using Holter monitoring. To assess the relationship between autonomic abnormalities and MRI all the patients underwent cranial and cervical spinal MRI.
Results: Our results showed that MS patients have decreased heart rate variability and diminished parasympathetic component of autonomic nervous system compared to controls. No significant association has been found between autonomic impairment in MS and the type and duration of the disease. There has been no significant relationship between MRI findings and autonomic involvement in MS.
Conclusion: MS patients have autonomic dysregulation against parasympathetic component, a condition which has no significant relationship with cranial and cervical spinal MRI findings.

Key words: Multiple sclerosis, autonomic nervous system, heart rate variability neuro imaging

Multipl Skleroz Hastalarinda Otonom Sinir Sistemi Tutulumu ve Kraniyal ve Servikal Spinal MRG Bulgulari İle İlişkisi

Özet

Amaç: Multiple sklerozis (MS), hastaların dizabilitelerinde önemli etkiye sahip olan otonomik disfonksiyon ile birlikte olabilir. Bu çalışmanın amacı MS hastalarında ve yaşa göre eşleştirilmiş kontrol grubunda standart otonomik testleri ve kalp hızı değişkenliğini kullanarak otonomik anormalliklerin sıklığını karşılaştırmaktı. Aynı zamanda, kraniyal ve servikal spinal manyetik rezonans görüntüleme (MRG) bulgularının otonomik testler ve kalp hızı değişkenliği ile olan ilişkilerini araştırmak da amaçlandı.

Metodlar: Yirmidört (% 68.6) relapsing-remitting, onbir (%31.4) sekonder progresif MS hastası ve 21 yaşa göre eşleştirilmiş kontrol çalışmaya alındı. Tüm deneklere parasempatik (Valsalva manevrasına, derin solumaya ve aktif postür değişikliğine kalp hızı yanıtları) ve sempatik (aktif postür değişikliğine kan basıncı yanıtları) fonksiyonları değerlendirmek amacıyla standart otonomik fonksiyon testleri ile birlikte 24-saatlik ve tilt testi sırasında Holter ile kalp hızı değişkenliği analizi uygulandı. Otonomik anormallikler ve MRG arasındaki ilişkiyi değerlendirmek için tüm hastalara kraniyal ve servikal spinal MRG yapıldı.

Sonuçlar: MS hastaları, kontrollere göre azalmış kalp hızı değişkenliği ve baskılanmış parasempatik otonomik sinir sistemi komponenti gösteriyorlardı. MS'de otonomik tutulum ile MRG bulguları arasında anlamlı bir ilişki bulunamadı.

Yorum: MS hastalarında, kraniyal ve servikal spinal MRG bulguları ile anlamlı ilişkisi olmayan parasempatik sinir sistemi aleyhine otonomik bozukluk mevcuttur.

Anahtar Kelimeler: Multiple sklerozis, otonom sinir sistemi, kalp hızı değişkenliği, nöro görüntüleme

INTRODUCTION

Multiple sclerosis (MS) which is a chronic inflammatory demyelinating disorder of the central nervous system (CNS) can be accompanied by symptoms of autonomic dysfunction[13]. Autonomic disturbances have an important impact on the disability of patients and can restrict daily activities in MS. Different groups concentrated on the effect of demyelinating lesion load on the presence and severity of autonomic dysfunction[14,24]. Some studies reported a relationship with autonomic disturbances and demyelinating brainstem lesions on Magnetic Resonance Imaging (MRI)[1,24,30] whereas others[2,7,10,22] could not confirm this association.

The aim of this study is to examine the frequency of autonomic abnormalities in MS patients and compare the results with age matched controls. We further evaluated the presence and activity of demyelinating lesions in different anatomical sites of CNS and searched whether there is any effect of demyelinating plaques on the results of autonomic tests.

MATERIAL AND METHODS

Subjects

Study population consisted of 35 patients diagnosed as MS by Mc Donald criteria[17] and 21 age-matched controls. Twenty-four (68.6%) patients had relapsing-remitting MS and eleven (31.4%) patients had secondary progressive MS. All patients had been free of exacerbations in the last four weeks during the study-time. None of the patients and controls was pregnant. They were not taking drugs that interfere with the autonomic function, none of them received caffeine or alcohol and did not have diabetes, prior cardiac disease or hypertension.

All the patients and control subjects were informed regarding the tests to be performed and verbal informed consent was taken from patients willing to enter the study. To minimize a possible interference

with systemic injection reactions, autonomic testing was done a day before the patient is supposed to inject immunomodulatory drugs and at least 36 hours after the last injection. Autonomic studies were performed on the MS patients in an air-conditioned laboratory with the room temperature maintained at 24°C. The patients were positioned supine on a manually operated tilt table with their arms supported on arm boards and abducted to 70–80° so that the point of measurement of blood pressure remained at the approximate level of the right atrium during tilting of the patient. Environmental noise, conversation and movement were reduced to minimum. The following battery of autonomic tests assessing parasympathetic function (heart rate responses to Valsalva maneuver, deep breathing, heart rate responses to active change of posture) and sympathetic vasomotor function (blood pressure responses to active change of posture) were employed to patients and controls. All subjects underwent 24-hour ambulatory and tilt table Holter monitoring.

Autonomic Tests

a. *Valsalva ratio:* After a resting period of 5 minutes the subject was asked to blow the hose of a mercury sphygmomanometer to a level of 30 mmHg for 15 seconds. Rhythm ECG was acquired both at baseline and during the maneuver as well as 40 beats after the completion of the test. The ratio of the longest RR interval after the maneuver to the shortest during the maneuver was calculated. A value below 1.45 for patients 41-60 years old and a value below 1.50 for patients below the age of 40 were considered abnormal[16].

b. *Deep breathing test:* The patient was asked to breathe deeply at a frequency of six breaths per minute each cycle being equally divided into inspiratory and expiratory phases. The difference between the longest RR interval and the shortest one in each cycle was calculated, results of six cycles were averaged and the so-called I-E difference was obtained. Differences below 15 bpm were considered abnormal[6].

c. *Heart rate response to active change of posture:* After a 5-minute resting period the subject was asked to stand up as quickly as possible. The ratio between the longest RR interval around the 30th beat after standing to the shortest RR around the 15th beat was obtained as 30/15 ratio. A value below 1.04 was considered abnormal[31].

d. *Blood pressure response to active change of posture:* Blood pressure was recorded both during 5- minute resting period and during standing. The differences in systolic and diastolic blood pressures after 2 minutes of erect position were determined and named as SBPACOP and DBACOP, respectively, which were then compared with across groups.

e. *24-hour holter recording:* 24 hour electrocardiographs of each subject were obtained to determine frequency and time domain parameters of heart rate variability (HRV) to examine the cardiac autonomic dynamics.

Analysis of heart rate variability parameters

HRV analysis was performed according to the Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology on HRV[27]. SYNESCOPE version 3.10 (ELA Medical) was used for all holter HRV analyses. All 24 hour, night and day-time periods were used to investigate HRV parameters. For the time-domain analysis of HRV, each QRS complex resulting from sinus node depolarization is detected, and normal-to-normal (NN) intervals are determined. The following standard parameters were calculated from the time series:

1-SDNN: Standard deviation of intervals between two normal R-waves. SDNN

gives an impression of the overall circulatory dynamics.

2-RMSSD: The square root of square of mean square differences of successive NN intervals. Higher values indicate higher vagal (parasympathetic) activity.

3-PNN50: The proportion derived by dividing NN50 (the number of interval differences of successive NN intervals greater than 50 ms) by the total number of NN intervals. Higher values indicate higher vagal (parasympathetic) activity.

4-PNN30: The proportion of NN30 (the number of interval differences of successive NN intervals greater than 30 ms) to total number of NN intervals. It is a measure of vagal (parasympathetic) activity.

Spectral analysis of HRV included: total power, high-frequency (HF) component (0.15–0.40 Hz), low-frequency (LF) component (0.04–0.15 Hz), and very low-frequency (VLF) component (0–0.04 Hz). The normalized high-frequency power (HF nu =100x high-frequency power/total power), normalized low-frequency power (LF nu = 100 x low-frequency power/total power), and low /high-frequency power ratio (LF/HF ratio= low-frequency power/high-frequency power) were calculated to give the relative changes in HRV in the frequency domain.

Heart rate variability measurement during tilt table testing:

Each subject underwent a 10-minute tilt table testing with a tilting angle of 70 degrees after a 10-minute resting period and holter recordings for both resting and tilting periods were obtained. Time and frequency domain analyses of HRV of both phases were performed for both MS patients and controls.

Cranial and Spinal MRI

Neuroimaging studies were performed using a 1.5 T scanner (Symphony, Siemens, Erlangen, Germany). All the patients underwent a routine cranial MRI including sagittal and transverse T1-weighted (W) spin-echo (SE) (TR/TE; 550/15 ms), transverse T2-W turbo SE (TR/TE; 4000/100 ms), transverse fluid-attenuated inversion-recovery (FLAIR) (TR/TE/TI; 8000/100/2100 ms) and postcontrast T1-W imaging with the same parameters as pre-contrast T1-W SE imaging at 5th minute upon intravenous administration of a Gd-based contrast media (0.1mmol/kg). Cervical spinal MRI was performed in each subject at the same or in a separate session and included T1-W SE (TR/TE; 500/15 ms) and T2-W turbo SE (TR/TE; 3200/90 ms) sagittal and axial images followed by postcontrast T1W imaging. In those who had both examinations at the same session, contrast media was administered upon completion of precontrast cranial and spinal imaging, and T1W imaging was repeated for brain and spinal cord respectively. Findings in cranial images were regarded as ‘supratentorial (ST)' or ‘infratentorial (IT)'. All MR studies were assessed visually for practical purposes. Total number of hyperintense lesions on T2W imaging and number of enhancing lesions in each compartment were counted by an experienced neuroradiologist (KKO). Enhancing lesions on postcontrast study were accepted as ‘active demyelinating-inflammatory' lesion. For practical purposes, number of the lesions were regarded as ‘category 1' for lesions <4, ‘category 2' for lesions between 5 and 9 and ‘category 3' if >9. Presence of cerebral, cerebellar or brainstem atrophy were noted from cranial MRI. The corpus callosum involvement was evaluated in terms of presence and number of T2-hyperintense lesions and atrophy. Lesions in the cervical spinal cord were regarded as brain stem lesions as well as atrophy and they were altogether composed ‘infratentorial' lesions and atrophy respectively. The cerebellum was distinguished from other anatomical IT structures in that symptoms of the

cerebellar lesions usually differ from those of the brain stem and cervical spinal cord.

Statistical Analysis:

All continuous variables were expressed as mean ± standard deviation. The comparison between continuous variables between groups was performed using Mann Whitney-U test. The categorical variables were compared by means of Chi square test; the fisher's exact test was utilized when the number of cases in any of the cells was fewer than five. The association between continuous variables was tested using bivariate analysis. A two-sided P value of <0.05 was considered statistically significant. The SPSS 11.0 pocket software (Chicago, IL, USA) was used for all statistical comparisons.

RESULTS

The demographic characteristics of the entire study population were given in Table **1**. There were no significant difference between the groups with respect to mean age and gender.

I. Heart Rate Variability and Autonomic Test Results

1. 24-Hour Heart Rate Variability Analysis (Table 2)

i. *Time domain analysis:* Time domain analysis in 24-hour period showed significantly lower PNN50 (10.48 ± 10.40 vs. 16.12 ± 11.23; p<0.05), PNN30 (22.53 ± 15.42 vs. 30.06 ± 14.11; p<0.05), and RMSSD (38.19 ± 28.74 vs. 45.72 ± 17.69; p<0.05) in the MS group when compared to controls.

ii. *Frequency domain analysis:* There were no significant difference between groups with respect to any parameter of the frequency domain analysis except for the total power (Tplnu), which was significantly lower in the MS group (7.98 ± 0.60 vs. 8.29 ± 0.74; p<0.05).

2. Heart Rate Variability Analysis during Tilt Testing (Table 3)

a. Supine Position

i. *Time domain analysis:* Time domain analysis in supine position was not significantly different between groups for any time domain parameter.

ii. *Frequency domain analysis:* Frequency domain analysis revealed that only total power (Tplnu) was significantly lower in the MS group when compared to controls (7.51±0.63 vs. 7.8±0.53;p<0.05).

b. Tilting

i. *Time domain analysis:* Time domain analysis showed significantly lower PNN50 (1.42±2.11 vs. 3.77±3.71; p<0.01), PNN30 (5.81±6.35 vs. 14.05±15.54; p<0.05), and RMSSD (16.6±6.3 vs. 25.93±19.52; p<0.01) in MS group compared to controls.

ii. *Frequency domain analysis:* Frequency domain analysis showed significantly lower HFnu (4.9±6.21 vs. 7.84±8.34; p<0.05) and LFnu (28.68±16.02 vs. 42.34±16.4; p<0.05) in MS group compared to controls.

3. Autonomic Tests (Table 4)

The number of subjects with an abnormal heart rate response to deep breathing test (20 vs. 4; p=0.01), heart rate response to active change of posture test (19 vs. 5; p<0.05), and the number of subjects with at least one parasympathetic test (28 vs. 10; p<0.05) were significantly higher in MS group compared to control group. There were no significant differences between groups regarding diastolic and systolic blood pressure response to active change of posture.

Table 1. Demographic Data of the Study Population

	MS Patients (N=35)	*Controls (N=26)*	*p*
Age (Years) (Mean±SD)	31.57±6.8	31.82±7.6	NS*
Gender (NO. of Male)	12 (34.3%)	9 (34.61%)	NS **
MS Type (NO. of Relapsing-Remitting MS)	24 (68.6%)	-	
EDDS (Mean±SD)	2.27±1.66	-	
Duration of Disease (Mean±SD)	5.94± 5.35	-	

* Mann-Whitney U Rank Sum Test
** Fisher's Exact Test

MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale

Table 2. The 24-Hour Heart Rate Variability Analysis in Patients with MS and The Controls (Mean±SD)

Parameter	*MS Patients (N=35)*	*Controls (N=26)*	*p**
TPLNU	7.98 ± 0.60	8.29 ± 0.74	< 0.05
LFnu	33.11 ± 8.07	37.91 ± 7.89	NS
HFnu	13.33 ± 8.62	16.25 ± 7.62	NS
LF/HF	3.51 ± 2.33	2.9 ±1.6	NS
SDNN	140.03 ± 45.55	132.64 ± 30.86	NS
PNN30	22.53 ± 15.42	30.06 ± 14.11	<0.05
PNN50	10.48 ± 10.40	16.12 ± 11.23	<0.05
RMSSD	38.19 ± 28.74	45.72 ± 17.69	<0.05

* Mann Whitney-U Rank Sum Test

Table 3. The Heart Rate Variability Analysis in Patients with MS and Controls in Supine Position and Upon Tilting (Mean±SD)

Parameter	*MS Patients (N=35)*		*Controls (N=26)*		*p**	
	Supine Position	Upon Tilting	Supine Position	Upon Tilting	Supine Position	Upon Tilting
TPLNU	7.51±0.63	7.78±0.72	7.8±0.53	7.78±1.07	<0.05	NS
LFnu	33.59±14.32	28.68±16.02	29.06±14.51	42.34±16.4	NS	<0.05
HFnu	15.24±13.14	4.9±6.21	15.64±13.29	7.84±8.34	NS	<0.05
LF/HF	3.39±2.31	11.44±9.55	2.83±1.87	8.48±5.14	NS	NS
SDNN	9.14±6.87	9.64±9.28	8.46±5.25	9.0±4.66	NS	NS
PNN50	11.53±17.22	1.42±2.11	17.38±21.13	3.77±3.71	NS	<0.01
PNN30	24.41±21.34	5.81±6.35	30.04±26.24	14.05±15.54	NS	<0.05
RMSSD	32.04±25.01	16.6±6.3	39.38±30.71	25.93±19.52	NS	<0.01

* Mann Whitney-U Rank Sum Test

Table 4. The Results of Autonomic Tests in Patients with MS and the Controls

Test	*MS Patients (N=35)*	*Controls (N=26)*	*P value*
[1]DB	20 (57%)	4 (15%)	< 0.05*
[1]ACOP	19 (54%)	5 (19%)	< 0.05**
[1]VS	13 (37%)	5 (19%)	NS
[1]AT LEAST 1 ABNORMAL PS TEST	28 (80%)	10(38%)	< 0.05**
[2]SBPACOP (mmHg) (Mean±SD)	-2.1 ± 17.1	3.27 ± 13.46	NS
[3]DBPACOP (mmHg) (Mean±SD)	0.71 ± 8.69	-0.72 ±7.15	NS

DB: heart rate response to deep breathing; ACOP: heart rate response to active change of posture; VS: heart rate response to Valsalva test; PS: parasympathetic; BP: blood pressure

[1] The Numbers in Each Cell Represent The Number of Patients with Abnormal Values; Percentages are Given in parenthesis

[2] Systolic Blood Pressure Response to Active Change of Posture (Mean± SD)

[3] Diastolic Blood Pressure Response to Active Change of Posture (Mean± SD)

* Fisher's Exact Test
** Chi Square Test

II. Cranial and Cervical Spine MRI Findings

On MRI 14 (40%) patients had less than 4 infratentorial hyperintense lesions, 15 (42.9%) had 5 to 9 lesions, and 6 (17.1%) had more than 9 lesions. Three (8.6%) of MS patients had less than 4 supratentorial MS lesions, 2 (5.7%) had 5 to 9 lesions, and 30 (85.7%) patients had more than 9 supratentorial lesions. Twenty-six (74.2%) patients had less than 4 cerebellar lesions, 8 (22.9%) had 5 to 9 lesions and 1 patient

(2.9%) had more than 9 lesions. Twelve patients (34.2%) had MS lesions in the corpus callosum. Six (17.1%) patients had "enhancing" lesions in infratentorial region, 14 (40%) patients had enhancing lesions in supratentorial region, and 4 (11.5%) patients had enhancing cerebellar lesions. One (2.9%) patient had cerebellar, 21 (60%) patients had corpus callosum, 16 (45.7%) patients had supratentorial, and 12 (34.3%) patients had infratentorial atrophy. Cervical spine MRI findings have been included in IT findings as mentioned in the methods.

III. Relationship between Heart Rate Variability Analyses, Autonomic Tests and MRI Findings

The statistical analysis of heart rate variability both in 24-hour and tilt table testing, autonomic tests and neuroimaging findings were evaluated. No relevant significance was found between the number of MS lesions (in IT, ST, corpus callosum and cerebellum) the IT atrophy, ST atrophy, cerebellum and corpus callosum atrophy, the activity of MS plaques and the heart rate variability parameters or autonomic tests.

IV. Relationship between Heart Rate Variability Analyses, Autonomic Tests, and Type and Duration of the Disease

There were no significant relationship between any of the employed tests and the type and duration of the disease (data not shown).

DISCUSSION

In various studies, it was showed that autonomic test abnormalities of MS patients can be variable and heterogeneous. This fact depends mainly on the relatively small sample sizes, different tests used to assess the autonomic nervous system, and the lack of standardization of the tests. However, the autonomic involvement in MS is well known[3-5,8]. Our study shows that MS patients have a diminished heart rate variability revealed by diminished total power in frequency domain in 24-hour heart rate variability analysis. MS patients also had decreased parasympathetic tone in 24-hour analysis indicated by decreased time domain figures of PNN50, PNN30, and RMSSD. The patient group as a whole did not demonstrate a significant difference in sympathetic measures of 24-hour heart rate variability analysis, which showed an intact sympathetic control of heart in this MS group. In tilt table testing both groups were similar in regard of heart rate variability parameters during resting whereas during tilting the MS group showed a significantly decreased parasympathetic tone compared to healthy controls as evidenced by decreased time domain parameters of parasympathetic origin. The patient group also demonstrated a significantly decreased sympathetic and parasympathetic tone than healthy controls indicated by decreased LFnu in tilting; however they demonstrated a significantly increased LF/HF ratio in tilt table testing showing that the parasympathetic impairment was more pronounced. Tracey et al., speculated that the dysfunction of parasympathetic nervous system, frequently presented in patients with autoimmune diseases, might be responsible for increased or altered activities of their immune systems[28].

Our heart rate variability analyses of both 24-hour and tilt table test data clearly demonstrates an imbalance between parasympathetic and sympathetic limbs of autonomic nervous system favoring the latter. This imbalance seems to result from diminished parasympathetic tone. Similar to our findings, in a study of rest-and-24-hour heart rate variability analyses of 34 MS patients LF, and LF/HF ratio were significantly higher in patient group in 24-hour power spectrum analysis, revealing an augmented sympathetic tone, independent of the disease duration or severity[20]. Autonomic dysfunction in MS has been widely studied by means of standard autonomic tests. Although the value of this battery of tests in certain disease states is

well appreciated there are conflicting data regarding the prevalence and type of autonomic dysfunction in affected population. The proportion of patients with MS with at least one abnormal cardiovascular autonomic test is high, pointing towards a prevalent dysautonomia. We found that 80% of MS patients in our study had at least one abnormal autonomic test. In a number of studies, more than half of the patients showed abnormal results to at least one cardiovascular test[1,2,11,18,23]. There are, however, also some studies with lower frequencies for at least one abnormal cardiovascular test[7,9,21].

Autonomic dysfunction defined by at least two abnormal responses to standard cardiovascular autonomic tests[19,26] has been reported over a wide range, from 8% to 70%[1,16,18,9,21,26] in MS population. The most common abnormalities were heart rate responses to deep breathing[1,2,18,24,25,30] and blood pressure response to handgrip (HG) test[4,29,30]. Heart rate response to active change of posture was also abnormal in a number of studies[1,4,9,21,24,26].

Most studies have reported bilateral involvement of autonomic nervous control of the cardiovascular system[11,12,15,23,24,30] whereas some studies reported impaired parasympathetic limb[9,18,25,26] and some others reported abnormal sympathetic limb[9,29]. Our results show that MS patients showed significantly impaired heart rate response to deep breathing and active change of posture and also the proportion of subjects with at least one abnormal parasympathetic test were significantly higher in patients with MS compared to controls. Valsalva test showed a trend towards impairment in patients with MS but lacked statistical significance. These findings show a parasympathetic impairment in patients with MS whereas, systolic and diastolic blood pressure responses to active change of posture were not different across both groups showing relatively spared sympathetic system.

Our results of MRI showed that the number and activity of MS lesions in central nervous system is not correlated to the autonomic tests or heart rate variability analysis in MS.

Our results are in accordance with most reports; however there are also reports which showed an association between MS lesions and autonomic tests[1,24,30]. Saari found a significant relationship between blood pressure responses to active change of posture and central nervous system lesions[24]. The possible explanation of the lack of association between CNS lesions and autonomic dysfunction may be the fact that autonomic dysfunction may result from abnormalities of supramedullary reflex pathways or spinal cord[7,22]. It is probable that MS plaques distributed throughout the brainstem and spinal cord may affect anatomically widespread autonomic regulatory areas and their connections[18].

In summary, our study has several conclusions: first, our study population with MS had decreased heart rate variability and a diminished parasympathetic component of autonomic nervous system compared to controls. This was reflected by diminished parasympathetic parameters of heart rate variability analysis both in a 24-hour basis and in tilt table testing as well as significantly abnormal autonomic tests of parasympathetic origin. The sympathetic tone, on the other hand, was spared relative to the parasympathetic tone; second, there is no significant association between autonomic impairment in MS and the type, duration of the disease and sex and the EDSS score; and third, there is no significant relationship between findings on cranial and cervical spinal MRI and autonomic involvement in MS.

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