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Predictability of Chronic and Persistent Lymphadenopathy in Childhood with Ultrasound and Laboratory Data: A Pediatric Hematology-Oncology Outpatient Clinic Experience

Çocukluk Çağı Kronik ve Persistan Lenfadenopatilerin Ultrason ve Laboratuvar Veriler Eşliğinde Öngörülebilirliği: Bir Çocuk Hematoloji-Onkoloji Polikliniği Deneyimi

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ABSTRACT

Aim: Our study aimed to investigate the factors that predicted laboratory and ultrasound findings for the lymph node to shrink to standard size.

Material and Method: The study examined lymphadenopathy cases (n=93) who applied to our pediatric hematology-oncology clinic between 2022 and 2023. The characteristics of cases with persistent lymph nodes and those without were compared.

Results: The diagnoses of 93 cases included in the study were reactive lymph node (n=76; 81.7%), infectious mononucleosis (n=9; 9.7%), tuberculosis (n=1; 1%), and lymphoma (n=2; 2%), and benign cytology (n=2; 2%). The median time to resolution of acute (n=8; 8.6%), subacute (n=26; 28%), and chronic (n=59; 63.4%) lymphadenopathy was 1 [5-155] week. In those with persistent lymphadenopathy, the mean hemoglobin value (g/dL) was lower (12.3±1.2 vs. 12.7±1.4, respectively) (p=0.047). The mean platelet value (334.2 ±108 vs. 288.4±89.5, respectively)(x10^3/mm^3)(p=0.047) was higher, and hilar vascularity on ultrasonography (1.6% vs 19.4%) (p=0.001) was lower compared to those without persistent lymphadenopathy. No relationship could be demonstrated between hypoechoic lymph nodes, blurred borders, necrosis, fatty hilus, perinodal cortical vascularity, cortical thickening, presence of lymph nodes in multiple regions, and lymph node disappearance.

Conclusion: This study is the first to mention that higher thrombocyte and lower hemoglobin levels may predict the persistency of lymphadenopathies and hilar vascularity as a sonographic feature indicates non-persistent lymphadenopathy.

Key Words: Lymphadenopathy, Ultrasonography, Hemoglobin, Platelets, Childhood

ÖZ

Amaç: Çalışmamızın amacı, laboratuvar ve ultrason bulgularının lenf nodunun normal boyuta inmesini öngören faktörlerin araştırılmasıdır.

Gereç ve Yöntem: Çalışmamızda, 2022-2023 yılları arasında çocuk hematoloji-onkoloji polikliğimize başvuran lenfadenopati olguları (n=93) incelendi. Persistan lenf nodu olan olgular ile olmayan olguların özellikleri karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 93 olgunun tanıları reaktif lenf nodu (n=76; %81,7), enfeksiyöz mononükleoz (n=9; %9,7), tüberküloz (n=1; %1), lenfoma (n=2; %2) ve benign sitoloji (n=2; %2) idi. Ortalama yaş ± standard sapma (SS); 8.2±4,4 yıl; kız sayısı 42 (%45,2) idi. Akut (n=8; %8.6), subakut (n=26; %28), kronik (n=59; %63,4) lenfadenopatinin ortanca kaybolma süresi 1 [5-155] hafta bulundu. Persistan lenfadenopatisi olanlarda, olmayanlara göre ortalama hemoglobin değeri (g/dL) (sırasıyla 12,3±1,2'e 12,7±1,4'e)(p=0,047) düşük, trombosit değeri (sırasıyla 334,2 ±108,0'e 288,4±89,5'e)(x10^3/mm^3)(p=0,047) daha yüksek, ultrasonografide hiler vaskülaritenin varlığı (%1,9'a %24)(p=0,001) daha düşük oranda istatistiksel anlamlı bulundu. Hipoekoik lenf nodu, sınır belirsizliği, nekroz, yağlı hilus, perinodal kortikal vaskülarite, kortikal kalınlaşma, birden çok bölgede lenf nodu varlığı ile lenf nodunun kaybolmaması arasında bir ilişki gösterilemedi.

Sonuç: Bu çalışma, yüksek trombosit ve düşük hemoglobin düzeylerinin lenfadenopatilerin kalıcılığını öngörmede, hilar vaskülaritenin ultrasonografik bir bulgu olarak ise persistan olmayan lenfadenopatiyi (<3 hafta) ön görebileceğini belirten ilk çalışmadır.

Anahtar Kelimeler: Lenfadenopati, Ultrasonografi, Hemoglobin, Trombosit, Çocuk

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Introduction

Cervical lymphadenopathy in children is usually reactive due to viral or infections such as mycobacterial infections. Lymphadenopathies are divided into three groups for their durations: acute (<3 weeks), subacute (3–6 weeks), or chronic (> six weeks) (1). Complete blood count, LDH (lactate dehydrogenase), uric acid, serologic tests, ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), or tissue sampling are considered in the case of complex cases. Patients with high-risk features, including age under 12 months, non-tender lymph nodes, size greater than 3 cm, supraclavicular location, and lack of regression, may require further investigation (2).

Persistent asymptomatic cervical lymphadenopathy does not usually require tissue sampling. In the study of Harris et al., pain, firmness, and lack of a normal fatty hilum on ultrasound were associated with the sampling decision. Of 197 patients, biopsies were performed in 30 (15.2%), of which 90% were benign. Reactive follicular hyperplasia, followed by atypical mycobacterial infection, were the most common pathologies. Serial ultrasound imaging resulted in a mean decrease of 0.34 cm. Abnormal ultrasound characteristics, such as the long to short axis, heterogenous echogenicity, and chaotic vascularity, are biopsy characteristics (3).

The most common malignant causes of cervical lymphadenopathy are neuroblastoma and leukemia in the first six years of life, Hodgkin's lymphoma, followed by non-Hodgkin lymphoma after six years. The sensitivity and specificity of Long diameter (L)/Short diameter (S)<2 values are 85% and 61%, respectively, for predicting malignancy (3). In the prospective study of Pandey et al., 120 cases of chronic lymphadenopathy lasting for at least one month had various infectious diagnoses like tuberculosis, fungal, and parasitic infections. The supraclavicular lymph nodes were associated with tuberculosis and malignancy. Tuberculosis has ultrasonographic features like strong internal echoes (calcification or hyalinosis in caseous necrosis), hypoechogenicity, matting, periadenitis, unsharp margins, and an echogenic thin layer (specific granuloma tissue layer). Compared with the adjacent muscles, the nodes with metastases are hypoechoic (4).

Our study aimed to determine the most common etiologies and potential predictors for chronicity and persistence of pediatric lymphadenopathies.

Material And Method

The children admitted to Duzce University's Pediatric Hematology-Oncology Policlinic with lymphadenopathies (n=93) between January 2022 and August 2023 were included in the study. Demographics, laboratory findings, and ultrasonographic findings were examined. This retrospective study compared the children's data with persistent lymph nodes (n=62) versus regressed to normal-sized lymph nodes (n=31). Duzce University Ethics Committee approved the study (Date: 2023, Number: 17).

Normal ranges for the lymph node's longest diameter are 1.5 cm for axillar and inguinal nodes and 1 cm for cervical nodes. The duration of lymphadenopathies is classified as acute (<3 weeks), subacute (3–6 weeks), or chronic (>6 weeks) lymph nodes. A lymph node size >2 cm after four weeks was defined as a persistent lymph node. The lymph nodes recovered (regressed to <2 cm) before four weeks were classified as non-persistent lymph nodes.

Fine needle aspiration indications were age less than 12 months, non-tender firm lymph nodes, size greater than 3 cm, location in the supraclavicular area, persistent systemic symptoms, lack of regression after observation, and response to antibiotic therapy.

Complete blood count, LDH (lactate dehydrogenase), uric acid, and serologies were studied in the laboratory. The pediatrician or pediatric hematologist-oncologist performed a physical examination. Ultrasonography revealed the changes and characteristics of the lymph nodes: localization, number, hilar vascularity, conglomeration or separation, long diameter, shape, echo, margin, necrosis, fatty-hilus, hilar vascularity, perinodal, cortical vascularity, cortex thickness, localization, and regions.

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze quantitative independent data. In the analysis of qualitative independent data, the Chi-Square and Fischer tests were used when the Chi-Square test conditions were not met. SPSS 28. 0 program was used in the analysis.

Results

Of 93 children with lymphadenopathies, the mean ± standard deviation (SD) age was 8.2 ± 4.4 years, and 42 (45.2%) were female. The most common etiologies were reactive lymphadenopathy (n=76; 81.7%) and infectious mononucleosis (n=9; 9.7%). Lymphoma, tuberculosis, and the pathologic finding of benign cytology were rarely determined. Eighty-five (91.4%) had no pathology in physical examination. The median [minimum-maximum] recovery time was 5 [1-144] months (Table 1).

Most of the lymphadenopathies (LAPs) (n=78; 83.9%) were bilateral, 45 (48.4%) consisted of ≥5 lymph nodes, 85 (91.4%) had iso-hyperechoic nodes, 86 (92.5%) had regular margins. None had an abscess, calcification, and perinodal fatty hyperechogenicity. Ultrasonographic findings are presented in Table 2.

Comparing the persistent and non-persistent LAP groups, chronic LAPs [47 (75.8%) vs. 12 (38.7%), respectively] were more common in the persistent group (p=0.001). The mean hemoglobin level (12.3±1.2 g/dl vs. 12.7±1.4) (p=0.047) was lower, and the mean thrombocyte level (334.2±108.0 vs. 288.4±89.5)(p=0.005) was higher in the persistent group than in the non-persistent group. Age, gender, physical examination, clinical findings, and other laboratories were statistically similar between the groups (Table 3). Fine needle aspiration or total resection revealed tuberculosis (n=1; 1%), lymphoma (n=2; 2%), and benign cytology (n=2; 2%).

Various ultrasonographic findings were compared between the groups, and hilar vascularity was significantly more common in the non-persistent (n=6; 19.4%) than the persistent group (n=1; 1.6%) (p=0.001). Posterior cervical LAP, number of lymph nodes, conglomerated, separated, even, small diameter, long diameter, shape, hypoechoic, iso-hyperechoic, lymph node, margin, necrosis, fatty-hilus, hilar vascularity, perinodal, cortical vascularity, hilus echogenicity, cortex thickness, supraclavicular, and multiples regions had statistically similar distributions between the groups (Table 4).

Discussion

In our small cohort of lymphadenopathies, the most common diagnoses were reactive lymphadenopathy and infectious mononucleosis. The following diagnoses were lymphoma, benign cytology, and suspected tuberculosis or tularemia. Most lymphadenopathies (LAPs) were bilateral, consisted of ≥5 lymph nodes, and had so-hyperechoic nodes and regular margins. None had apse, or calcification. Also, Riga et al. reported that most cases with neck masses had reactive lymphadenopathies (65.8%), congenital/ developmental cysts were present in 28.9%, and

Table 1. Clinical features of children with lymphadenopathy.

Features		Median [Min-Max]	Mean±SD/n-%	
Age (years)		7 [1-17]	8.2 ±	4.4
Gender	Female		42 54.8%	45.2%
	Male		51	54.8%
Diagnosis				
• Infectious mononucleosis			9	9.7%
• Reactive lymphadenopathy			76	81.7%
• Lymphoma			2	2.2%
• Tuberculosis			1	1.1%
• Benign cytology			2	2.2%
• Unknown			3	3.2%
Physical examination and clinic features				
Finding (-)			85	91.4%
Finding (+)			8	8.6%
• Hepatomegaly			5	5.4%
• Splenomegaly			1	1.1%
• Fever			1	1.1%
• Erythema in the lymph node region			1	1.1%
Antibiotics	• (-)		58	62.4%
	• (+)		35	37.6%
Biopsy	• (-)		89	95.7%
	• (+)		4	4.3%
Recovery time (months)		5 [1-144]	14.5 ±	26.5

Table 2. Ultrasonographic findings of patients with lymphadenopathies.

Features		n	%
Laterality	Unilateral	14	15.1%
	Bilateral	78	83.9%
	NA	1	1.1%
Posterior cervical lymphadenopathy	(-)	67	72.0%
	(+)	25	26.9%
	NA	1	1.1%
Number of nodes	1	2	2.2%
	2-4	45	48.4%
	≥5	45	48.4%
	NA	1	1.1%
Conglomerated LAP	(-)	90	96.8%
	(+)	2	2.2%
	NA	1	1.1%
Separated LAP	(-)	17	18.3%
	(+)	75	80.6%
	NA	1	1.1%

Equality in size distribution	(-)	27	29.0%
	(+)	65	69.9%
	NA	1	1.1%
Short diameter	0	1	1.1%
	<10 mm	58	62.4%
	≥10 mm	32	34.4%
	NA	2	2.2%
Maximum long diameter	0	6	6.5%
	<2 cm	26	28.0%
	2-3 cm	44	47.3%
	≥3 cm	11	11.8%
	NA	6	6.5%
Shape	Oval	73	78.5%
	Elonge	16	17.2%
	Round	3	3.2%
	NA	1	1.1%
Echogenicity compared to vault	Hypoechoic	7	7.5%
	Iso-hyperechoic	85	91.4%
	NA	1	1.1%
Lymph node	Homogeneity	86	92.5%
	Heterogeneity	5	5.4%
	NA	2	2.2%
Margin	Regular	86	92.5%
	Irregular	5	5.4%
	NA	2	2.2%
Necrosis	(+)	2	2.2%
	(-)	89	95.7%
	NA	2	2.2%
Fatty hilus	(+)	5	5.4%
	(-)	86	92.5%
	NA	2	2.2%
Hilar vascularity	(+)	7	7.5%
	(-)	72	77.4%
	NA	14	15.1%
Perinodal cortical vascularity	(+)	1	1.1%
	(-)	90	96.8%
	NA	2	2.2%
Hilus echogenicity	(+)	67	72%
	(-)	21	22.6%
	NA	5	5.4%
Cortex enlargement	(+)	30	32.3%
	(-)	57	61.3%
	NA	6	6.5%

Supraclavicular	(+)	2	2.2%
	(-)	52	55.9%
	NA	39	41.9%
In various regions	(+)	10	10.8%
	(-)	40	43.0%
		43	46.2%

LAP: lymphadenopathy, NA: Non-available.

Table 3. Comparing the features and laboratories of the persistent LAM group with the non-persistent group.

Features		Persistent n=(62)				Non-persistent (n=31)				p
		Mean±SD/n-%			Median	Mean±SD/n-%			Median	
Age		7.5	±	4.0	7.0	9.6	±	4.9	8.0	0.056*
Gender	Female	25		40.3%		17		54.8%		0.185**
	Male	37		59.7%		14		45.2%		
Physical examination										
Finding (-)		58		93.5%		27		87.1%		0.296**
Finding (+)		4		6.5%		4		12.9%		
Hepatomegaly		4		6.5%		1		3.2%		
Splenomegaly		0		0.0%		1		3.2%		
Fever		0		0.0%		1		3.2%		
Tenderness and redness on lymph nodes		0		0.0%		1		3.2%		
Clinical Findings										
Duration	Acute	3		4.8%		5		16.1%		0.001**
	Subacute	12		19.4%		14		45.2%		
	Chronic	47		75.8%		12		38.7%		
Antibiotic administration	(-)	38		61.3%		20		64.5%		0.762**
	(+)	24		38.7%		11		35.5%		
Biopsy	(-)	61		98.4%		28		90.3%		0.106**
	(+)	1		1.6%		3		9.7%		
Laboratories										
Hemoglobin (g/dl)		12.3	±	1.2	12.1	12.7	±	1.4	12.9	0.047*
Neutrophils (/mm^3)		4628	±	2417	4030	3676	±	1600	3600	0.094*
Thrombocyte (x10^3/mm^3)		334.2	±	108.0	334.0	288.4	±	89.5	279.0	0.005*
Sedimentation (mm/h)		18.7	±	18.8	12.5	11.9	±	8.8	9.0	0.098*
CRP (mg/L)		0.46	±	1.7	0.07	0.24	±	0.65	0.07	0.791*
LDH (U/L)		242	±	53.6	231	266	±	131	230	0.671*
Uric acid (mg/dl)		3.3	±	0.94	3.3	3.8	±	1.1	3.7	0.072*
Ultrasonographic findings										
Unilateral		9		14.8%		5		16.1%		0.862*
Bilateral		52		85.2%		26		83.9%		
Unknown		1		1.6%		0		0%		

LAP: lymphadenopathy, NA; Not available, CRP: C- reactive protein, LDH: lactate dehydrogenase.

*: Mann-Whitney U test, **: X^2 Chi-Square test.

Table 4. Comparing the ultrasonographic features of the persistent LAM group with the non-persistent LAM group.

		N	%	n	%	
Posterior cervical LAP	(-)	43	69.4%	24	77.4%	0.480*
	(+)	18	29%	7	22.6%	
	NA	1	1.6%	0	0	
Number of lymph nodes	1	2	3.2%	0	0.0%	1.000*
	2-4	29	47.5%	16	51.6%	
	≥5	30	48.3%	15	48.4%	
	NA	1	1.6%	0	0	
Conglomerated	(-)	60	96.8%	30	96.8%	1.000*
	(+)	1	1.6%	1	3.2%	
	NA	1	1.6%	0	0	
Separated	(-)	9	14.5%	8	25.8%	0.197*
	(+)	52	83.9%	23	74.2%	
	NA	1	1.6%	0	0	
Even	(-)	18	27.9%	9	29.0%	1.000*
	(+)	43	70.5%	22	71.0%	
	NA	1	1.6%	0	0	
Small diameter	<10 mm	37	59.7%	21	67.8%	0.516*
	≥10 mm	23	37.1%	9	29.0%	
	NA	2	3.2%	1	3.2%	
Long diameter	<2 Cm	14	22.6%	12	38.7%	0.062*
	2-3 Cm	35	56.4%	9	29%	
	≥3 Cm	6	9.7%	5	16.1%	
	NA	7	11.3%	5	16.1%	
Shape	Oval	49	79.1%	24	77.4%	0.858*
	Elonge	10	16.1%	6	19.4%	
	Round	2	3.2%	1	3.2%	
	NA	1	1.6%	0	0	
Echo	Hypoechoic	5	8.2%	2	6.5%	0.765*
	Iso-hyperechoic	56	91.8%	29	93.5%	
	NA	1	1.6%	0	0	
Lymph node	Homogeneous	58	95.1%	28	90.3%	1.000*
	Heterogeneous	3	4.9%	2	6.5%	
	NA	1	1.6%	1	3.2%	
Margin	Regular	57	93.4%	29	93.6%	1.000*
	Irregular	4	6.6%	1	3.2%	
	NA	1	1.6%	1	3.2%	
Necrosis	(-)	61	98.4%	28	90.3%	0.106*
	(+)	0	0.0%	2	6.5%	
	NA	1	1.6%	1	3.2%	
Fatty-hilus	(-)	58	93.5%	28	90.3%	1.000*
	(+)	3	4.9%	2	6.5%	
	NA	1	1.6%	1	3.2%	

Hilar vascularity	(-)	53	85.5%	19	61.2%	0.001*
	(+)	1	1.6%	6	19.4%	
	NA	8	12.9%	6	19.4%	
Perinodal, cortical vascularity	(-)	60	96.8%	30	96.8%	1.000*
	(+)	1	1.6%	0	0	
	NA	1	1.6%	1	3.2%	
Hilus echogenicity	(-)	14	22.6%	7	22.6%	0.966*
	(+)	45	72.6%	22	71%	
	NA	3	4.8%	2	6.4%	
Cortex thickness	(-)	36	58%	21	67.7%	0.339*
	(+)	22	35.5%	8	25.8%	
	NA	4	6.5%	2	6.5%	
Supraclavicular	(-)	38	61.3%	14	45.2%	1.000*
	(+)	2	3.2%	0	0.0%	
	NA	22	35.5%	17	54.8%	
In various regions	(-)	32	51.6%	8	25.8%	0.053*
	(+)	5	8%	5	16.2%	
	NA	35	56.4%	18	58%	

LAP: lymphadenopathy, NA: Not available.

*: Chi-Square test.

5.3% had tumors (6). Our findings were consistent with Meadows et al.'s study of 98 young children (8). The current study found that 52 (%53) had normal lymph nodes, 40 (40.8%) had reactive lymph nodes, 1 (%1) had abnormal lymph nodes, and 3 (3.1%) were indeterminate.

In one retrospective study, Park et al. reported that the diagnoses were Kikuchi disease, reactive hyperplasia, lymphoma, and suppurative lymphadenitis. Perinodal fat hyperechogenicity, heterogeneous echotexture, a short diameter of the most prominent lymph nodes, and loss of fatty hilum were significant ultrasonography findings in cervical lymphadenopathy (5). Our study concluded that hypervascularity in the lymph node was essential for predicting absolute recovery. However, other features (perinodal, cortical vascularity, hilus echogenicity, cortex thickness, supraclavicular, and multiple regions) were not differentiating properties for predicting the persistency of lymphadenomegaly.

In one similar report to our study, Alves et al. reported that reactive lymphadenopathies were the most common cases, with the following diagnosis of congenital/ developmental cysts. Tumors were 5.3% of the population. This study revealed that rigid and fixed mass in the neck does not always address a malignancy. Also, Alves et al. found that round and larger nodes may be expected (7). Meadows et al. showed that palpable lymph nodes, despite the reduction of <1 cm, are not signs of malignancies. Most cases of lymphadenopathy recover simultaneously, and a careful follow-up is an adequate strategy (8). Our study concludes that most patients with persistent nodes do not address malignancies or chronic hematologic disease. The children without additional features may not be frequently followed up.

The red flag features are lymph nodes ≥2 cm, axillary/ supraclavicular nodes ≥1 cm, firm, fixed nodes, rapid enlargement of lymph nodes, generalized lymphadenopathy weight loss, fever, night sweats, malaise, breathlessness, pallor, and hepatosplenomegaly (8). Signs of tuberculosis on ultrasound are the ultrasonic signs of hilus absence, S/L ratio ≥ 0.5, unclear edge, necrosis, echogenic thin layer, strong echoes, and capsular or peripheral vascularity (9). Uncomplicated lymph nodes have normal only central hilar vascularity; however, malignant nodes have central and peripheric vascularity (10). Hypoechoic (compared with adjacent musculature), flattened or oval-shaped lymph nodes with hyperechoic linear hilum, and internal vessels from the hilum are benign (10-12).

A normal lymph node is characterized by an elliptical structure with a hypoechoic halo and central sharp linear hyperechoic fatty hilum containing a single vessel. In ultrasonography, reactive nodes are enlarged and hypoechoic with well-defined borders and widened hilum. Bilateral head and neck nodes with adenoidal or tonsillar hypertrophy are features of infectious etiologies. Doppler imaging reveals a more extensive, rounder, more vascular, symmetric radial pattern of the vessels. Leukemia lymph nodes are defined as discrete, localized, or generalized, with slightly conglomerated enlarged nodes. An eccentric hilum may show nodal cellular infiltration. In other malignancies except for leukemia, the metastatic lymph nodes do not have an echogenicity in the hilum and can have sharp borders (12). Lindeboom et al. pointed to the sonographic features of marked decreased echogenicity, liquefaction with intranodal cystic necrosis, nodal matting, and adjacent soft-tissue edema were observed in non-tuberculosis associated mycobacterium infections (13). Our study adds to the literature that acute lymph nodes have significantly more common findings of hilar vascularity as a predictor of resolution.

Viral etiologies (Infectious mononucleosis) may have concomitant thrombocytopenia and anemia due to bone marrow suppression (14). Anemia and thrombocytopenia were more common in non-infectious diseases than infectious diseases and more significantly in the malignants than the non-malignants (15). Our study concluded that in 100% of cases, reactive (81.7%) lymph nodes and infectious mononucleosis (9.7%) were

the leading diagnoses that were similarly distributed among the groups. However, thrombocyte levels were significantly increased, and hemoglobin levels were significantly decreased in the persistent group than in the non-persistent group.

Conclusion

Lower hemoglobin and higher thrombocyte levels suggest persistent lymphadenopathies. However, a sonographic feature of hilar vascularity in the lymphadenopathy was associated with non-persistent lymphadenopathies. As far as we searched, this conclusion was not reported in the literature.

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