Correspondence

Serum Cytokine Levels in Postinfective Fatigue Syndrome

To the Editor—[Q1]Previous studies have sought evidence for a role of abnormal cytokine activity in patients with chronic fatigue syndrome and have had conflicting results [1–3]. These ambiguous results may reflect heterogeneity in groups of patients considered to have chronic fatigue syndrome and variations in assay systems. We established postinfective fatigue syndrome as the only well-characterized model of the onset and evolution of chronic fatigue syndrome in a prospective cohort of individuals followed up from the onset of acute infection (Dubbo Infection Outcomes Study [DIOS]) [4]. Longitudinally collected clinical data and blood samples from participants in DIOS provide a unique opportunity for nested case-control studies examining the pathophysiology of chronic fatigue syndrome. We previously reported the lack of association between cytokine production from cultured peripheral blood mononuclear cells and the postinfective fatigue syndrome–related illness in participants in DIOS [5]. We now report a masked analysis of a longitudinal case-control series from DIOS that extended the number of cytokines tested and focused on serum levels.

Twenty patients with acute infection were selected, including 5 patients with serologically confirmed acute Epstein-Barr virus (EBV) infection followed by postinfective fatigue syndrome lasting ⩾6 months, 5 patients with acute infection (not primary EBV but seropositive for EBV) followed by postinfective fatigue syndrome, and 10 matched control subjects with acute EBV infection followed by prompt recovery. Serum samples and clinical data from baseline and from 3–6 months and 9–12 months after onset of infection were analyzed. Serum samples were coded according to case-control status before transfer to the cytokine analysis laboratory.

Thirty-five analytes were measured in serum samples with use of a multiplex immunoassay, including the chemokines [Q2]epithelial cell–derived neutrophil-activating peptide 78, eotaxin, growth-regulated oncogene α, interleukin (IL)–8, interferon (IFN)–inducible protein 10, monocyte chemotactic protein 3, monokine induced by gamma IFN, macrophage inflammatory protein 1α, macrophage inflammatory protein 1β, and regulated upon activation normal T cell expressed and secreted; the cytokines IFN-γ, IL-1α, IL-1β, IL-1Ra, IL-4, IL-5, IL-6, IL-7, IL-2, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IL-17F, tumor necrosis factor α, tumor necrosis factor β; and the growth factors nerve growth factor, platelet-derived growth factor β, transforming growth factor β, vascular endothelial growth factor, fibroblast growth factor β, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor.

All of the study groups were predominantly female and were matched for both sex distribution (by χ^2 test, $P = .670$) and age (by analysis of variance, $P = .597$). Cytokine data were analyzed by 2-way analysis of variance examining the effects of time and type of case (EBV postinfective fatigue syndrome, non-EBV postinfective fatigue syndrome, or control) and by Spearman's correlation between symptom scores and cytokine levels. Because of the number of parameters tested, a conservative threshold for statistical significance ($P < .005$) was used. Results are shown in Table 1[Q3].

Although there were changes in cytokine levels over time (generally elevated at baseline), there were no statistically [Q4]significant differences in serum levels of any of the cytokines at any time between patients with postinfective fatigue syndrome and control subjects. Our study does not support the hypothesis of a role for abnormal cytokine activity in the pathogenesis of postinfective fatigue syndrome or chronic fatigue syndrome.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.[Q5]

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References

1. Cameron B, Bharadwaj M, Burrows J, et al. Prolonged illness following EBV infection is associated with altered immunity but not elevated viral load. J Infect Dis **2006**; 193:664–71.
2. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med **2002**; 64: 604–11.
3. Lorusso L, Mikhaylova SV, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. Autoimmun Rev **2009**; 8:287–91.
4. Hickie I, Davenport T, Wakefield D, et al.; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ **2006**; 333:575.
5. Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, et al. Post-infective fatigue syndrome is not associated with altered cytokine production. Clin Infect Dis **2007**; 45:732–5.

Table 1. Serum Cytokine Levels in Participants in the 3 Study Groups Over Time

	Serum cytokine level, mean pg/mL ± SD		
Cytokine, group	Baseline	3–6 months	12 months
ENA-78			
Control subjects	29 ± 25	28 ± 21	34 ± 25
Patients with EBV PIFS	18 ± 10	17 ± 8	13 ± 7
Patients with non-EBV PIFS	21 ± 21	26 ± 20	20 ± 15
Eotaxin			
Control subjects	12 ± 6	12 ± 6	13 (8)
Patients with EBV PIFS	16 ± 4	18 ± 4	17 ± 4
Patients with non-EBV PIFS	10 ± 4	9 ± 3	11 ± 8
G-CSF			
Control subjects	3 ± 1	2 ± 1	2 ± 1
Patients with EBV PIFS	7 ± 11	7 ± 10	9 ± 12
Patients with non-EBV PIFS	4 ± 6	2 ± 2	8 ± 12
GRO-α			
Control subjects	8 ± 4	6 ± 2	7 ± 3
Patients with EBV PIFS	10 ± 7	8 ± 3	6 ± 4
Patients with non-EBV PIFS	6 ± 6	3 ± 1	3 ± 3
IFNγ			
Control subjects	2 ± 1	1 ± 1	1 ± 1
Patients with EBV PIFS	1 ± 1	1 ± 1	1 ± 1
Patients with non-EBV PIFS	18 ± 38	2 ± 3	23 ± 51
IL-12p40			
Control subjects	4 ± 3	3 ± 2	3 ± 2
Patients with EBV PIFS	6 ± 6	6 ± 5	4 ± 3
Patients with non-EBV PIFS	2 ± 2	2 ± 1	1 ± 1
IL-15			
Control subjects	8 ± 6	8 ± 4	7 ± 4
Patients with EBV PIFS	10 ± 9	6 ± 5	8 ± 6
Patients with non-EBV PIFS	21 ± 2	8 ± 1	24 ± 1
IL-17			
Control subjects	1 ± 2	0	0
Patients with EBV PIFS	2 ± 4	2 ± 2	2 ± 2
Patients with non-EBV PIFS	1 ± 1	0	0
IL-17F			
Control subjects	60 ± 153	42 ± 110	48 ± 97
Patients with EBV PIFS	19 ± 21	6 ± 7	9 ± 10
Patients with non-EBV PIFS	159 ± 318	77 ± 145	33 ± 44
IL-1α			
Control subjects	6 ± 2	5 ± 1	4 ± 2
Patients with EBV PIFS	6 ± 3	4 ± 2	3 ± 2
Patients with non-EBV PIFS	5 ± 5	3 ± 1	3 ± 1
IL-1RA			
Control subjects	1 ± 1	1 ± 2	2 ± 3
Patients with EBV PIFS	1 ± 2	2 ± 2	4 ± 5
Patients with non-EBV PIFS	6 ± 9	2 ± 3	4 ± 7
IL-2			
Control subjects	1 ± 2	0	0
Patients with EBV PIFS	1 ± 1	0 ± 1	0 ± 1
Patients with non-EBV PIFS	9 ± 19	1 ± 2	8 ± 18
IL-6			
Control subjects	1 ± 1	0	4 ± 8
Patients with EBV PIFS	1 ± 1	6 ± 10	5 ± 10
Patients with non-EBV PIFS	1 ± 3	0 ± 1	2 ± 5
IL-7			
Control subjects	3 ± 2	2 ± 1	2 ± 1
Patients with EBV PIFS	3 ± 1	3 ± 0	4 ± 1
Patients with non-EBV PIFS	2 ± 1	2 ± 1	2 ± 1

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Table 1. *(Continued.)*

Cytokine, group	Serum cytokine level, mean pg/mL ± SD		
	Baseline	3–6 months	12 months
IL-8			
Control subjects	2 ± 4	0 ± 1	3 ± 3
Patients with EBV PIFS	5 ± 10	6 ± 8	1 ± 3
Patients with non-EBV PIFS	0	0	3 ± 4
IP-10			
Control subjects	279 ± 176	164 ± 138	135 ± 148
Patients with EBV PIFS	265 ± 230	118 ± 80	77 ± 59
Patients with non-EBV PIFS	983 ± 2050	79 ± 42	53 ± 35
Leptin			
Control subjects	2689 ± 3074	2876 ± 2555	2754 ± 2896
Patients with EBV PIFS	2189 ± 2819	2093 ± 2710	3072 ± 3598
Patients with non-EBV PIFS	5371 ± 8942	3817 ± 2635	2263 ± 2400
MCP-3			
Control subjects	4 ± 2	3 ± 2	3 ± 2
Patients with EBV PIFS	5 ± 3	4 ± 1	5 ± 3
Patients with non-EBV PIFS	7 ± 9	3 ± 2	9 ± 12
MIG			
Control subjects	3100 ± 1495	554 ± 360	324 ± 241
Patients with EBV PIFS	2435 ± 2354	1649 ± 1929	198 ± 137
Patients with non-EBV PIFS	569 ± 894	200 ± 131	95 ± 106
MIP-1α			
Control subjects	15 ± 28	5 ± 15	108 ± 205
Patients with EBV PIFS	57 ± 76	440 ± 746	480 ± 1034
Patients with non-EBV PIFS	1 ± 2	3 ± 6	1 ± 3
MIP-1β			
Control subjects	15 ± 15	10 ± 7	46 ± 62
Patients with EBV PIFS	31 ± 30	73 ± 59	85 ± 155
Patients with non-EBV PIFS	9 ± 4	9 ± 5	11 ± 7
NGF			
Control subjects	13 ± 10	15 ± 6	12 ± 7
Patients with EBV PIFS	17 ± 9	12 ± 7	16 ± 10
Patients with non-EBV PIFS	29 ± 47	10 ± 10	37 ± 66
PDFGBB			
Control subjects	4007 ± 1637	4507 ± 1652	4641 ± 2281
Patients with EBV PIFS	3372 ± 2247	3912 ± 1490	5758 ± 1366
Patients with non-EBV PIFS	3288 ± 2349	4138 ± 1927	3284 ± 2274
RANTES			
Control subjects	133 ± 40	197 ± 127	132 ± 32
Patients with EBV PIFS	132 ± 57	253 ± 290	164 ± 99
Patients with non-EBV PIFS	167 ± 105	134 ± 32	137 ± 39
TGFβ			
Control subjects	1 ± 3	2 ± 4	0 ± 1
Patients with EBV PIFS	0	0	0
Patients with non-EBV PIFS	3 ± 4	0 ± 1	3 ± 6
VEGF			
Control subjects	40 ± 34	29 ± 22	41 ± 33
Patients with EBV PIFS	44 ± 21	37 ± 15	53 ± 29
Patients with non-EBV PIFS	22 ± 11	21 ± 17	25 ± 24

NOTE. EBV, Epstein-Barr virus; ENA, epithelial cell–derived neutrophil-activating peptide; G-CSF, granulocyte colony-stimulating factor; GRO, growth regulated oncogene; IFN, interferon; IL, interleukin; IP, IFN–inducible protein; MCP, monocyte chemotactic protein; MIG, macrophage inflammatory protein; NGF, nerve growth factor; PDFGBB, PIFS, postinfective fatigue syndrome; RANTES, regulated upon activation normal T cell expressed and secreted; SD, standard deviation; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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