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Brief report

Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): Indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut–intestinal permeability

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Abstract

There is now evidence that chronic fatigue syndrome (CFS) is accompanied by immune disorders and by increased oxidative stress.

The present study has been designed in order to examine the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. *Hafnia alvei*; *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae* in CFS patients, patients with partial CFS and normal controls.

We found that the prevalences and median values for serum IgA against the LPS of enterobacteria are significantly greater in patients with CFS than in normal volunteers and patients with partial CFS. Serum IgA levels were significantly correlated to the severity of illness, as measured by the FibroFatigue scale and to symptoms, such as irritable bowel, muscular tension, fatigue, concentration difficulties, and failing memory.

The results show that enterobacteria are involved in the etiology of CFS and that an increased gut–intestinal permeability has caused an immune response to the LPS of gram-negative enterobacteria. It is suggested that all patients with CFS should be checked by means of the IgA panel used in the present study and accordingly should be treated for increased gut permeability.

Keywords: Chronic fatigue syndrome; Inflammation; Immunity; Autoimmune; IgA; Enterobacteria; Gut permeability; Oxidative stress; Leaky gut

1. Introduction

There is now some evidence that chronic fatigue syndrome (CFS) is accompanied by immune disorders and by increased oxidative stress. Immune activation is suggested by an increased expression of T lymphocyte activation markers, such as CD26 and CD38 and alterations in cytokine production. Poor cellular immunity is suggested by lowered natural killer cell cytotoxity, decreased mitogen-induced lymphocyte responses and

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defects in early T cell activation. Inflammatory reactions are indicated by decreased serum zinc levels and increased serum concentrations of the alpha2 globulin fraction (review: Maes et al., 2005, 2006).

Increased oxidative stress in CFS is suggested by increased levels of isoprostanes and oxidized low density lipoproteins (Kennedy et al., 2005), higher LDL thiobarbituric acid reactive substances (TBARS) and decreased anti-oxidative defences, such as lower serum zinc and dehydroepiandrosterone-sulphate (Vecchiet et al., 2003; Maes et al., 2005, 2006).

The occurrence of CFS may not only be triggered by viral and bacterial infections, stressful life events and physical stress, type III–IV allergies for food and heavy metals, but also by an increased permeability of the gut barrier (Maes, 2005).

The present study has been carried out in order to examine whether CFS is accompanied by an increased permeability of the gut barrier whereby an immune response is mounted to endotoxins secreted by gram-negative enterobacteria.

2. Subjects and methods

2.1. Subjects

Forty subjects participated in the present study, 11 unrelated controls (staff or their family members), and 29 patients admitted to the M-Care4U Outpatient Clinics, Belgium. We made the diagnosis of CFS by means of the Centers for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994). Patients with chronic fatigue but not fulfilling all diagnostic CFS criteria were classified as suffering from partial CFS. The severity of CFS was measured by means of the FibroFatigue scale, i.e. the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (Zachrisson et al., 2002). The inclusion and exclusion criteria have been presented elsewhere (Maes et al., 2005, 2006). Patients and controls gave written informed consent after the study protocol was fully explained. The study has been approved by the local ethical committee.

3. Methods

Fasting blood was sampled during the morning hours for the determination of the IgM and IgA against the LPS of 7 different enterobacteria (see Table 1). The analyses were performed by means of an indirect ELISA method according to the methods outlined by the manufacturer (Gemacbio, The Ultimate Biopharmaceuticals, France) and described previously (Geffard et al., 2002). Each serum sample was measured in duplicate and tested simultaneously with three standard solutions. The optical densities (OD) of the three standards are expressed as Z values. The biological interassay CV values are <10%.

4. Statistics

Relationships between variables were assessed by means of Pearson's product moment correlation

Table 1
Age and gender distribution and the measurements of serum IgM and IgA levels against the LPS of *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri* and *Klebsiella pneumoniae* in normal controls, patients with partial CFS and patients with CFS

Variables		Normal controls	Partial CFS	CFS	F or x	p value (df=2/37)
Age sex		41.5 (10.4)	41.4 (11.0)	44.5 (10.4)	F=0.4	0.7
		3/8	4/10	5/10	χ=0.13	0.9 (df=2)
Hafnia alvei	IgM	−0.46 (1.12)	−0.19 (1.24)	0.20 (1.32)	F=0.9	0.6
	IgA	−0.84 (0.61)	−0.40 (0.55)	0.43 (1.59)***	F=4.7	0.01
Pseudomonas aeruginosa	IgM	−0.45 (1.23)	−0.10 (0.96)	0.75 (1.53)	F=3.1	0.054
	IgA	−0.02 (1.20)	0.45 (1.69)	2.66 (3.33)***	F=5.0	0.01
Morganella morganii	IgM	−0.25 (0.96)	−0.03 (1.07)	0.76 (1.80)	F=1.6	0.2
	IgA	−0.78 (0.51)	−0.08 (1.13)	2.03 (3.65)***	F=5.2	0.01
Proteus mirabilis	IgM	−1.18 (1.52)	0.22 (1.27)*	0.90 (1.49)**	F=6.9	0.003
	IgA	−0.94 (0.82)	0.19 (1.20)	2.95 (4.33)***	F=6.9	0.003
Pseudomonas putida	IgM	−0.19 (0.92)	0.50 (1.60)	1.44 (1.68)**	F=3.9	0.02
	IgA	−0.45 (0.58)	0.31 (1.21)	3.82 (4.53)***	F=8.5	0.001
Citrobacter koseri	IgM	−0.14 (1.09)	0.39 (1.82)	0.94 (2.10)	F=1.2	0.3
	IgA	−0.44 (0.54)	0.04 (1.11)	3.54 (4.11)***	F=9.5	0.0007
Klebsiella pneumoniae	IgM	−0.69 (0.74)	0.71 (1.76)	1.58 (3.15)**	F=3.3	0.047
	IgA	−0.92 (1.99)	0.28 (1.10)	1.89 (2.61)**	F=6.3	0.004

All results are shown as mean (±SD).
*Significantly different from normal controls at p<0.01; **significantly different from normal controls at p<0.05; ***significantly different from normal controls and partial CFS at p<0.05 (all results of Dunn tests).