Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome

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Submitted: November 5, 2007 *Accepted: November 21, 2007*

Key words: **chronic fatigue syndrome; intestinal mucosal dysfunction; leaky gut; leaky gut diet; oxidative stress; immunoglobins intravenously; antioxidants**

Neuroendocrinol Lett 2007; **28**(6):739–744 **PMID:** 18063928 NEL280607A13

Abstract

There is now evidence that chronic fatigue syndrome (CFS) is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut and indicates intestinal mucosal dysfunction (IMD). Here we report a case of a 13 year old girl with CFS who showed very high values for serum IgM against the LPS of some enterobacteria and signs of oxidative and nitrosative stress, activation of the inflammatory response system, and IgG3 subclass deficiency. Upon treatment with specific antioxidants and a "leaky gut diet", which both aim to treat increased gut permeability, and immunoglobins intravenously, the increased translocation of the LPS of gram negative enterobacteria normalized and this normalization was accompanied by a complete remission of the CFS symptoms.

Recently, we have shown that gram-negative enterobacteria may play a role in the etiology of chronic fatigue syndrome (CFS) [1]. We detected an increased IgM and IgA response to the lipopolysaccharide (LPS) of different enterobacteria in CFS. These results were interpreted to indicate an increased gut-intestinal permeability in CFS which in turn allows an increased translocation of LPS from gram-negative enterobacteria through the gut wall. The latter, in turn, causes an immune response directed against the translocated LPS. This condition is also described as leaky gut and indicates intestinal mucosal dysfunction [1]. Accordingly, we suggested that CFS patients should be treated for leaky gut by specific antioxidants such as glutamine, N-acetyl cysteine and zinc [1].

Here we report a case of a 13 years old girl. November 10, 2006, she entered our consultation room sitting in a wheel chair because she was unable to walk or stand due to muscle pain and weakness. The symptoms had begun in January 2005 after a common pharyngitis. The symptoms did not

CASE REPORT

reside and she developed progressive muscle weakness, muscle hypotonia, abdominal bloating, headache, and concentration and sleep disorders. There was a weight loss of 10 kg in a few months (from 57 kg to 47 kg). Since a Belgian University Department of internal medicine detected a mycoplasma infection, she was treated with Biclar. But, at the same time the internal specialists suspected a strong "psychogenic component" and sent her to the Department of Psychiatry. Fortunately, the parents did not follow this advice and went to another University Department specialized in CFS. There, they found a number of inflammatory markers, such as: increased serum IgM and increased leukocyte elastase activity, increased PKR activity, and RNAse activity and lowered natural killer cell activity, which was as low as 8.4%. These are well-known biomarkers for CFS [2]. In addition, very low serum IgG3 levels (14 mg/dL) and a lactose intolerance could be detected, as well as increased serum IgM levels to the LPS of gram negative bacteria (Table 1, 04-06-2005). Consequently, the correct diagnosis of CFS due to gut dysbiosis was made. She then was treated with Ciproxine 500 mg tid, for 10 days a month, to be repeated during several months. However, due to further symptoms of muscle weakness, "paralysis" and a further weight loss of 4 kg she was admitted into another hospital for nutritional treatment by the second co-author of this study. The latter, found also a stomach paresis, another biomarker for CFS. When the nutritional parameters were more or less normalized she was send to the Department of Neurology for further examination. The latter showed: normal EMG and MRI of the brain, and an aspecific type II muscle fiber atrophia (muscle biopsy of the M. quadriceps femoris). Therefore, the neurologists posited that a mild axonal type of Guilain-Barré syndrome might be present. Their main diagnosis, however, was "conversion hysteria". The latter was based on the symptom "la belle indifference", established by the senior neurologist. In their referral letter they stated that "the previous CFS specialist of course made the diagnosis of CFS", but in no way, they could even consider CFS as a possible diagnosis.

We could register the following symptoms: fatigue, muscle weakness, impossibility to walk or to stand, muscle contractions, sore throat, tender lymph nodes, abdominal complaints (bloating), malaise, nausea, vertigo, concentration difficulties and failing recent memory, sleep disorders and unrefreshing sleep, headache, and repeated subjective experiences of infection. Thus, the patient fulfilled the diagnosis of CFS according to the Centers for Disease Control and Prevention (CDC) criteria [3]. The first author of this paper, a psychiatrist, could not detect anything as "la belle indifference". What we saw was a young lady who was very ill and suffered from her illness and not being able to go to school and meet with her friends.

Blood analyses revealed a number of immune disorders, i.e. with reference to the normal limits as established for these analytes in accredited laboratories: low serum IgG3 (11 mg/dL), increased serum immune complexes (C1Q=25 µg Eq/mL), increased serum IgM (392 mg/dL), complement C3 (148 mg/dL), and antibody levels against gangliosides (GT1b-IgM), and somewhat increased microsomial TPO antibodies (68 IU/mL). There were signs of increased oxidative and nitrosative stress (O&NS) and damage caused by O&NS to fatty acids, DNA and proteins, i.e. high oxydized LDL-antibodies (>1 200 µU/mL), increased excretion of 8-OH-desoxyguanosine (32.1 µg/g creatinin), and increased serum IgM levels directed against phosphatidyl inositol, nitro-cysteinyl, and serum bovine albumin [4]. A number of anti-oxidants were significantly decreased, i.e. plasma free carnitine (14.5 µmol/L), total carnitine (20.3 µmol/L), acylcarnitine (5.8 µmol/L) and coenzyme Q10 (CoQ10; 42.3 µg/L). Finally, we found also decreased levels of the T3-poly-unsaturated fatty acids, eicosapentanoiac acid (EPA) and docosahexaeenic acid (DHA), which constitute other biomarkers for CFS [5]. A repeated measurement of the IgM responses directed against the LPS of gram-negative enterobacteria showed very high IgM responses (Table 1; 08-06-2005). These results show a very severe translocation of the LPS of gram-negative enterobacteria and, thus, suggest a very severe IMD, which was more pronounced than some months earlier. Our diagnosis was: chronic fatigue syndrome (as far as this label is adequate: see further) caused by IMD, damage due to O&NS, a lowered antioxidant status, and activation of the inflammatory response system (IRS) with an autoimmune response.

We started our treatment (10-11-2005) which consisted of: antioxidants, i.e. a mixture of L-carnitine, CoQ10, lipoic acid, and taurine; and another supplement consisting of substances that are known to treat gut permeability, consisting of L-glutamine, gamma oryzanol, zinc, etc. In addition, we started a specific "leaky gut diet" (Maes, Van Nunen and Heynssens, unpublished data; the diet can be requested from the corresponding author). We also started a treatment with intravenous immunoglobulins (IVIg), i.e. sandoglobuline 6 g/day during 1 month, and thereafter 6 g each two weeks for the following months [6].

During the next few moths, i.e. from December 2005 to May 2006, no change in the clinical picture could be detected. The IgM values against LPS remained very high but were already significantly lower than before starting the treatment (Table 1; 13-01-2006 and 22-03-2006).

However, August 18, 2006 the patient walked in into our consultation room. She told us that she regained strength, that her concentration was much better and could read books again, and that her sleep disorders were much better. She had restarted her swimming classes. She still suffered from a non-refreshing sleep and abdominal complaints. The IgM response against LPS again was improved (Table 1, 18-08-2006).

The next consultation, December 8, 2006, learned that her clinical condition was again much better: she could study and could concentrate just as before her illness. Her sleep became refreshing and the abdominal complaints including bloating were better although sometimes she

had diarrhea and nausea. During one week she had suffered from sore throat and tender lymph nodes. The IgM responses to LPS were considerably attenuated (Table 1; 15-11-2006), indicating less severe IMD. Blood analyses showed that the immune complexes and serum IgM levels and other inflammatory markers had normalized. Also, plasma L-carnitine and CoQ10 levels and the urinary excretion of 8-OH-desoxyguanosine had normalized, although plasma oxidized LDL antibodies were still increased.

February 1, 2007 she told us that in January she had returned to school and took part in swimming and fitness classes. She ascertained that all her symptoms had disappeared and that she felt just as good as before her illness. We then stopped IVIg but continued the antioxidants and the leaky gut diet, although we had to motivate the patient to continue with it.

July 13, 2007 she was very proud to tell us that she finished the school year with a very good score (>80%). Table 1 (26-06-2007) shows that the IgM responses were normalized. By now – November, 2007 – all CFS symptoms are still in remission.

DISCUSSION

This patient fulfilled the diagnostic symptomatic criteria for CFS [3], i.e. the patient had a severe chronic fatigue of longer than six months; and suffered from more than four symptoms, i.e. substantial impairment in short-term memory or concentration, sore throat, tender lymph nodes, muscle pain, headache of a new type, pattern or severity, unrefreshing sleep, and post-exertional malaise lasting more than 24 hours. Although these diagnostic criteria are now well established, many specialists – neurology and internal medicine in this case report – still miss and dismiss this diagnosis. They rather conclude that patients with this medical disorder suffer – in accordance with Freud's non-scientific theories – from "conversion symptoms with a strong psychogenic component", a symptom complex which could not be detected by the first author, a skilled psychiatrist. It is common practice in our Benelux countries that those patients then are referred to a psychiatrist to undergo the mainstream treatment for that condition, i.e. psychodynamic therapies. This means that patients with severe medical disorders are being treated as having a mental illness with "a nonsense treatment" that does not treat anything. Even worse, in Belgium, some doctors who treat CFS are prosecuted by the national health care insurances, e.g. by the Christian Mutualiteit (CM). In another Benelux country, the Netherlands, scientists and professors who work on psychoneuroimmune disorders in CFS are called quacks by an anti-quack organization, which is officially supported by the Ministery of Health – since previous ministers or their deputies directly took part in this organization. Phrased differently, the Dutch Ministery of Health supports anti-quacks to blame academicians of being quacks because they consider CFS (and other medical illnesses such as postnatal depression) as a medical disorder. The above are indeed organized attempts of the political world to try to eliminate the scientific view that CFS is a medical disorder. The official acceptance of the latter obviously would mean that the national health care systems are obliged to financially support those patients who now are considered hypochondriacs and, therefore, may easily be suspended from the national health care systems.

One of the above diagnostic criteria implies that the patient has to have a severe chronic fatigue of longer than six months while no other known medical condition could explain the CFS. However, using specific biomarkers, which we described above, a specific organic disorder may be observed, characterized by intracellular inflammation, O&NS and damage due to O&NS, and an increased translocation of the LPS of gram-negative bacteria and sometimes auto-immunity. This means

Table 1. Measurement of serum IgM against the LPS of 6 different gram negative bacteria during treatment with antioxidants, leaky gut diet and intravenous immunoglobulins. The treatment was started 11-10-2005.

Variables	06-04-2005	08-06-2005	13-01-2006	22-03-2006	18-08-2006	15-11-2006	26-06-2007
Hafnia Alvei	3.9	12.8	6.8	7.6	7.5	5.6	1.8
Pseudomonas Aeruginosa	0.4	4.5	5.6	4.7	4.4	2.6	1.6
Morganella Morganii	5.8	9.4	6.2	5.6	4.7	3.1	2.4
Pseudomonas Putida	5.5	11.4	10.6	8.7	8.5	9.8	2.2
Citrobacter Koseri	3.5	9.3	5.7	4.7	3.4	3.3	2
Klebsiella Pneumoniae	1.8	16.2	7.1	6.8	4.3	2.2	2.2
Total sum	20.9	63.6	42	38.1	32.8	26.6	12.2

The measurements are shown as standard deviations. The analyses are performed by means of an indirect ELISA method according to the methods outlined in [1]. Each serum sample was measured in duplicate and tested simultaneously with three standard solutions. Results are considered normal when <3.0 SD. The total sum gives an indication of the total "LPS translocation load", i.e. the mounted IgM-related response to the translocated LPS from the 6 different bacteria [1].

that the diagnosis CFS according to the CDC criteria cannot be used when the known biomarkers described above are measured. Therefore, the diagnostic criteria should be adapted to meet the new findings that CFS has a specific organic pathophysiology.

There is now some evidence that CFS is accompanied by an activation of the IRS, including signs of poor cellular immunity; and by increased O&NS [review: 4,7,8]. Also, this patient showed signs of activation of the IRS, such as: increased serum IgM; immune complexes; complement C3; microsomial TPO antibodies; anti ganglioside GT1b IgM antibodies; leukocyte elastase activity, PKR activity, and RNAse activity and lowered natural killer cell activity. She also showed signs of O&NS and a lowered antioxidant status, such as increased oxydized LDL-antibodies; 8-OH-desoxyguanosine; and serum IgM levels directed against phosphatidyl inositol, nitrocysteinyl, and serum bovine albumin; and decreased plasma free L-carnitine; total carnitine; acylcarnitine and CoQ10.

As previously discussed by us, the different immune findings in CFS, e.g. activation of the IRS, intracellular inflammation, O&NS, autoimmunity, etc. may be related to the increased translocation of LPS of gram-negative bacteria [1]. Thus, the trigger factors of CFS, e.g. infections – in this case report a mycoplasma infection –, psychological stress, and physical exhaustion may have induced IRS activation and O&NS [1]. Inflammation may – through an increased production of interferon-gamma (IFNγ) and interleukin-6 (IL-6) - cause a loss of the epithelial barrier function [9–11]. This in turn may cause normally poorly invasive enterobacteria to exploit lipid raft-mediated transcytotic pathways to cross the intestinal epithelium, and these effects may precede cytokine-induced disruption of tight junctions [9–11]. This increased translocation of the LPS of enterobacteria may then mount an immune response against the LPS of gram-negative enterobacteria thereby aggravating preexisting inflammation and O&NS in CFS or – when primary – induce inflammation and consequently CFS. We have discussed previously, that different trigger factors, such as psychological stress, viral and bacterial infections, physical exhaustion and leaky gut, may cause induction of nuclear factor kappa beta (NFκβ), the major upstream, intracellular mechanism which regulates inflammatory and O&NS mediators [12], such as cyclo-oxygenase (COX-2) and inducible NO synthase (iNOS). Indeed, we found that the production of NFκβ, COX-2 and iNOS is significantly higher in patients with CFS than in normal controls [12,13]. The translocated LPS of the gram-negative enterobacteria may induce a) NFκβ, COX-2 and iNOS, and consequently, the IRS and O&NS; and b) TOLL-like receptors, which may activate the PKR pathway [14]. These mechanisms could explain the occurrence of IRS activation and the increased PKR activity in this patient. It is also known that systemic LPS causes chronic central neuroinflammation. Thus, systemic LPS results in rapid brain tumor necrosis factor-α (TNFα) increases, which remain elevated for 10 months, and activate brain microglia to produce chronically elevated pro-inflammatory factors [15]. It is well-known that a central neuroinflammation with increased production of pro-inflammatory cytokines, such as TNFα, is accompanied by the sickness behaviour complex [15]. This mechanism could also explain the sleep disorders, cognitive disorders, anorexia and frank weight loss in this patient. Moreover, increased gut permeability may also explain the occurrence of autoimmunity in CFS, such as against gangliosides, as found in this case report [1,17,18]. Enterobacteria may act as superantigens for T lymphocytes or may induce autoimmunity through a mechanism called molecular mimicry [19,20]. Indeed, these enterobacteria have antigenic sites very similar to those of neuronal tissue and its lipid structures. These antigens will go into various tissues and trigger inflammation and once autoantibodies are formed the inflammation may become more chronic. Similar causal mechanisms have been presented to occur in Guillain-Barré syndrome [17], a diagnosis which was considered by the neurologist in this case report, although he did not measure ganglioside antibodies. Thus, systemic LPS caused by an increased translocation not only induces peripheral inflammation and O&NS, but may also induce a longstanding central neuroinflammation and autoimmune responses directed against neurons.

This patient also had an IgG3 subclass deficiency, a condition which is over-represented in patients with CFS (Maes et al. in preparation) and is related to recurrent infections, environmental allergies, and autoimmune responses [21,22]. Therefore, it may be hypothesized that the IgG3 subclass deficiency had increased the risk to develop CFS since it induces an increased propensity towards infections, IRS activation and autoimmune responses.

During the combined treatment with antioxidants, the "leaky gut diet", and IVIg, the translocation of LPS from gram negative bacteria decreased and normalized which was accompanied by an attenuation of most of the IRS and O&NS variables measured by us. There is now some evidence that specific antioxidants, e.g. glutamine [23], N-acetyl-cysteine [24], and zinc [25,26], show a significant efficacity in the treatment of increased gut permeability. Since our patient showed signs of O&NS and damage due to O&NS, such as lipid peroxidation, damage to DNA and proteins, and decreased antioxidant defences, we administered a specific antioxidant mixture based on L-carnitine, CoQ10, lipoic acid and taurine. These substances are known to: inhibit oxygen radical formation; help protect tissues from O&NS damage; protect mitochondria from oxidative damage; improve mitochondrial function; increase energy levels in the mitochondria through β-oxidation and, thus, function as mitochondrial nutrients; modulate immune function; and have cyto- and neuroprotective activities [27–30]. It is our expertise that – in order to restore IMD – the above antioxidants should be combined with a "leaky

gut diet" consisting of milk allergic, gluten-free and low-carb diet. The latter sometimes should be combined with an exclusion diet, based on the elimination of dietary allergens. This is comparable with rheumatoid arthritis patients who sometimes show leaky gut and may develop aggravation of the symptoms as a result of allergens in their diet [31]. In this respect, we should also point toward the finding of a lactose-intolerance in our patient.

Since our patient had also lowered IgG3 serum levels and signs of inflammatory and autoimmune reactions, we also started a treatment with IVIg. Indeed, IVIg have usually been administered for replacement therapy of humoral immunodeficiencies, including common variable hypogammaglobulinemia and IgG subclass deficiencies [32]. IVIg shows a significant efficacy in preventing respiratory symptoms and in treating recurrent bronchitis and asthma in hypogammaglobulinemic patients [32]. Moreover, IVIg are now also widely used as immunomodulators because of their efficacy in treating inflammatory and autoimmune disorders. The exact mechanism of action by which IVIg are of benefit in these immune disorders is only partly understood. There is now some evidence that IVIg may attenuate cytokine-induced NFκβ production; inflammation and the production of IFNγ and IL-6; may exhibit immunomodulatory effects on T-cell activation; modulate and promote the immune response; neutralize infectious agents; favour phagocytosis; and inhibit LPS-stimulated cytokine production [33–37]. Secondly, IVIg contain antiidiotypic antibodies against human autoantibodies, which may explain its efficacy in treating autoimmune disorders [38]. Last but not least, IVIg may decrease bacterial translocation beyond the mesenteric lymph nodes, i.e. IVIg protects the intestinal ecological equilibrium by decreasing bacteria overgrowth in the intestinal microflora; decreases the number of translocated bacteria; and prevents bacterial translocation spread [39]. Thus, IVIg may be useful to treat IMD because IVIg decrease bacterial translocation beyond the mesenteric lymph nodes; have anti-inflammatory effects; and attenuate the production of pro-inflammatory cytokines that may induce IMD, i.e. IFNγ and IL-6; neutralize microorganisms; favour phagocytosis; and inhibit LPS-stimulated cytokine production. The above working mechanisms may explain why our treatment with antioxidants, the "leaky gut diet" and IVIg is able to attenuate IRS activation, reverse O&NS and may decrease LPS translocation, which all together have lead to a normalization of the IMD after some months of treatment.

In conclusion, in this case report, we show that the normalization of the increased translocation of gram-negative enterobacteria – obtained with a specific diet, specific antioxidants and IVIg – is accompanied by an attenuation or normalization of IRS activation and O&NS and by a clinical remission.

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