REVIEW & CASE REPORT

Chronic Fatigue Syndrome: la bête noire of the Belgian Health Care System

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Abstract

The World Health Organization acknowledges Myalgic Encephalomyelitis (ME)/ Chronic Fatigue Syndrome (CFS) to be a medical illness. ME/CFS is characterized by disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways.

In 2002, the Belgian government started with the development of CFS "Reference Centers", which implement a "psychosocial" model. The medical practices of these CFS Centers are defined by the Superior Health Council, e.g. treatment should be based upon Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET); and biological assessments and treatments of ME/CFS should not be employed.

Recently, the Belgian government has evaluated the outcome of the treatments at the CFS Centers. They concluded that a "rehabilitation therapy" with CBT/GET yielded no significant efficacy in the treatment of ME/CFS and that CBT/GET cannot be considered to be curative therapies.

In case reports, we have shown that patients who were "treated" at those CFS centers with CBT/GET in fact suffered from IO&NS disorders, including intracellular inflammation, an increased translocation of gram-negative enterobacteria (leaky gut), autoimmune reactions and damage by O&NS. Considering the fact that these findings are exemplary for ME/CFS patients and that GET may even be harmful, it means that many patients are maltreated by the Belgian CFS Centers.

Notwithstanding the above, the government and the CFS Centers not only continue this unethical and immoral policy, but also reinforce their use of CBT/GET in patients with ME/CFS treated at those Centers.

Introduction

Myalgic Encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS) is a disorder associated with several related biochemical and immunological abnormalities in multiple inflammatory, and oxidative and nitrosative stress (IO&NS) pathways (Maes, 2009). These pathways encompass: 1) immune activation; 2) intracellular inflammation; 3) viral and bacterial infections; 4) dysfunctional mitochondria; 5) lowered anti-oxidant status; 6) increased oxidative and nitrosative stress (O&NS), resulting into damage to DNA, essential fatty acids, proteins, mitochondria and red blood cells; and 7) increased translocation of gram-negative bacteria (leaky gut) (Maes *et al.* 2006a; 2006b; 2007a; 2007b; 2007c; 2007d; 2007e; 2008; 2009b; Lorusso *et al.* 2009; Spence *et al.* 2008;

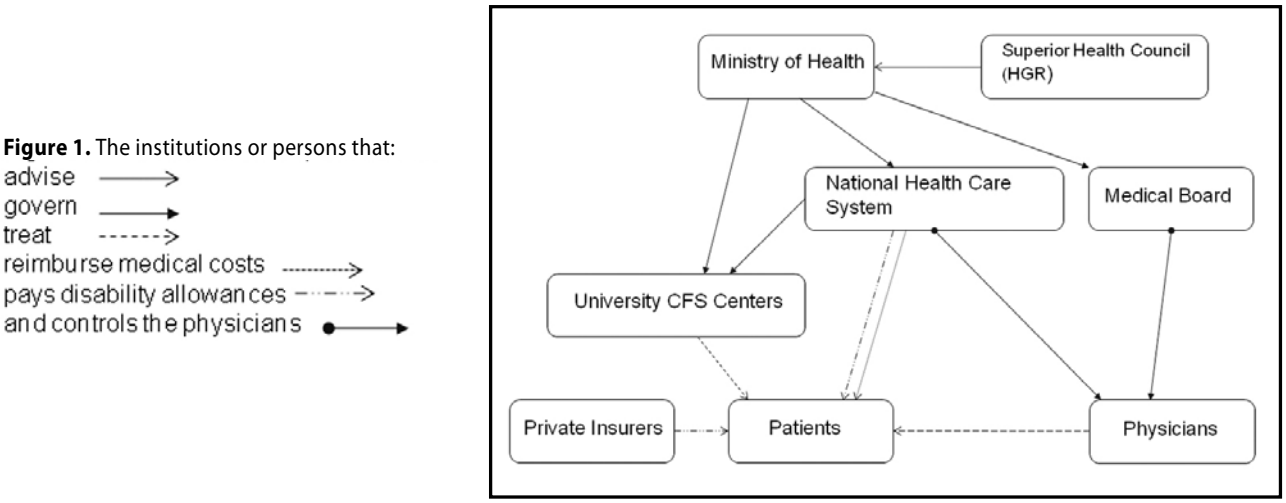

Figure 1. The institutions or persons that:

Aspler *et al.* 2008; Kerr *et al.* 2008; Buchwald *et al.* 1997; Nijs *et al.* 2005).

The Belgian Ministry of Social Affairs and Health started 6 years ago with the installment of CFS "Reference Centres" at the Belgian Universities. The medical practices of these CFS Centers have been defined by the statements of the Belgian Superior Health Council (HGR, de Hoge Gezondheidsraad), which is governed by the Minister of Social Affairs and Health. The Superior Health Council is the link between the government policy and the scientific world in the field of public health (Superior Health Council, 2008). See *Figure 1* for the governmental institutes described in this paper.

The report (no 8338) of the Superior Health Council (2008) states that 1) the treatment of CFS should be based on Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET); and 2) biological assessments and treatments should not be employed. The Superior Health Council (2008) states that CFS fits the model of a "biopsychosocial model", with biological and psychosocial components that influence each other. However, the biological aspects are minimized in such a way that it seems as if they are not there. Biological abnormalities are declared to be non-existent or irrelevant for the pathophysiology of ME/CFS. In fact, the Superior Health Council (2008) and thus the Ministry of Social Affairs and Health takes no effort to highlight the identification of existing research on the biological aspects of ME/CFS. The only thing that is recommended over and over again is the need for more research on CBT and GET, while no recommendations are made for biological research into ME/CFS. This creates the image that ME/CFS is a mental condition and that the only approach for dealing with ME/CFS is CBT/GET. So, in fact the Ministry and the National Health Care System do not employ a "biopsychosocial" model but rather a "psychosocial" model.

Outcome studies on CBT and GET at the CFS Reference Centers

The Belgian Health Care Knowledge Center (KCE) is "a semi-governmental institution which produces analyses and studies in the different research domains in which decisions must be taken; collecting and disseminating objective information from registered data, literature and current practice; and developing high level scientific expertise" (The Belgian Health Care Knowledge Center, KCE, 2008). The missions of the Belgian Health Care System (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering, RIZIV, 2006) are to organize 1) the compulsory insurance for medical care; 2) the disability allowances; and 3) the information to caregivers about the rules of the compulsory health insurance.

It is now clear from the abovementioned reports (Belgian National Health Care System, 2006) that the CFS Centers have failed in their primary missions. The "objective assessment data" show that the treatment with CBT/GET at those CFS Centers is not effective. Although an increased employment rate was a primary outcome measure, the employment rate was even decreased after the "rehabilitation" program. The cardiopulmonary capacity was not significantly ameliorated by the treatment. The review states that given the results, the physical exertion capacity can not constitute an adequate test to measure the success rate of CBT/GET therapies (page 54). Moreover, the methods of this study were less than adequate: the authors appear to have used post-hoc statistical analyses in an open-label study with many missing values and without a control group of ME/CFS patients who were treated with guided support group or placebo. Moreover, the Belgian National Health Care System (2006) did not give any data on the number of "responders to treatment" as defined by for example "full recovery" or a reduction of 50% in ME/CFS symptoms as measured by a validated ME/CFS rating scale based on a (semi)structured interview. An overview of the Tables with the results in the abovementioned reports shows that there are only modest effects in some, but not all, self-rated symp-

toms. The results of this "study" with CBT/GET at the CFS Reference Centers suggest that there are virtually no patients who had recovered from ME/CFS. In their discussion of the results, the Health Care Knowledge Center (KCE, 2008) and the Belgian National Health Care System (2006) then acknowledge that the CBT/GET treatments at the CFS Centers yielded insufficient results, but at the same time they continue to discuss studies, which were published by other authors, in an attempt to suggest that CBT/GET could have an effect in treating ME/CFS. The Belgian Government has proven and admits that CBT/GET cannot be considered to be a curative therapy to treat ME/CFS (Commissie voor de Volksgezondheid, het Leefmilieu en de Maatschappelijke Vernieuwing, 2007). Overall, the treatment results obtained at the CFS Centers, the methods of collecting their research data, the statistical analyses of the results and the duplicate discussions of the same results by the Health Care Knowledge Center and the Belgian National Health Care System are not only disappointing, but also inadequate. Even worse, it is impossible to formulate any scientific guideline for the diagnoses and treatments of ME/CFS from the experience at the CFS Reference Centers.

The only interesting point of the CFS Reference Centers is that they have provided evidence that CBT/GET has no clinical benefits in the treatment of ME/CFS. Since the "(bio)psychosocial" model has been systematically applied in the abovementioned CFS Reference Centers, we can conclude that this model is not applicable for treating ME/CFS. Also, patient inquiries carried out in the United Kingdom, Scotland and the Netherlands have shown that CBT/GET has no significant impact (15–30%) or that the condition of the patients is even further deteriorated (approx. 40–60%). Only in a very small group (15–35%), CBT/GET was successful (Action for ME/AfME, 2001; CFS/ME Working Group, 2002; Action for ME/AfME, 2007; Koolhaas *et al.* 2008). Thus, the "success rate" is not much higher than that obtained by standard care alone or a self-chosen therapy (20–30%).

Critical notes on the CFS Reference Centers and the Ministry of Social Affairs and Health

The reports of the Superior Health Council (No 8338) (2008), the Health Care Knowledge Center (2008) and the National Health Care System (2006) do not mention that the scientific output of the CFS Reference Centers is negligible. Not only no landmark paper was published by the CFS Centers, but even the number of published articles is particularly low. Nevertheless, the CFS Centers are financially supported by the Ministry and it appears that the CFS Reference Centers received some thousands euro of governmental funds per patient "treated". For example, four of these CFS Centers have hired 23.26 full time equivalents on a yearly basis (Belgische Kamer van Volksvertegenwoordigers, 2007). One would think that these CFS Centers would at least publish a few papers on their CBT/GET treatments. But no study measuring the impact of CBT/GET was published by those CFS Centers, although they had the financial means and the patients to carry out such studies. Therefore, it is incomprehensible to see that, although the clinical results achieved by these Centers are as good as nil, their only recommendation is to conduct more research into CBT/GET, alone or together, and individually or in groups. Apparently, not enough money has been wasted on the useless treatments in those CFS Centers.

The recent recommendation of the Superior Health Council (No 8338) (2008); the Health Care Knowledge Center (2008) and the National Health Care System (2006) actually are at right angles to the international state-of-the-art on ME/CFS (Maes, 2009). The guidelines from the Superior Health Council are amongst others that even established biochemical markers of ME/CFS may not be used (page 9); ME/CFS patients should be treated with CBT/GET only (page 11); and there is no evidence to employ immunological therapies, e.g. immunoglobulins intravenously (IVIg), biochemical therapies and food supplements (page 12). The reports of the above Institutes do not refer to the relevant literature: studies on the biochemical and immunological abnormalities in ME/CFS are ignored, although more than 3,500 papers are reporting on the biochemical abnormalities in large subgroups of patients with ME/CFS. Moreover, Belgium has two prominent researchers in the field of immunological abnormalities in ME/CFS, i.e. dr. K. de Meirleir and dr. M. Maes. Both were not invited to participate in these CFS Centers. The internationally recognized scientists and physicians who work biochemically, but are not affiliated with the CFS Reference Centers, not only receive no financial support, but their research is silenced or ridiculed.

There are now several publications in the Medline, which demonstrate that specific immune therapies and natural anti-inflammatory and anti-oxidative substances (NAIOSs), are useful in the treatment of ME/CFS and fatigue (Strayer *et al.* 1994; Lerner *et al.* 2007; Endresen, 2003; Maes and Leunis, 2008; Maes *et al.* 2008; 2009b; Vermeulen and Scholte, 2004; 2006; Plioplys and Plioplys, 1997). Also, translational experiments have demonstrated the value of specific NAIOSs to treat fatigue and muscle pain (Gupta *et al.* 2009; Singh *et al.* 2002a; 2002b; Kuratsune *et al.* 2002; Kuo *et al.* 2009). It is clear that the Ministry of Social Affairs and Health consciously ignores the scientific data concerning the biochemical and immunological pathophysiology of ME/CFS and evidence-based or promising therapies.

The composition of the committees appointed to deal with ME/CFS, for example the CFS working group of the Superior Health Council is composed of people who internationally have little relevance in the field. The chairman of the committee is a psychiatrist who has published not one peer-reviewed scientific article

on ME/CFS in the last 8 years. The "experts" who were appointed are mainly strong advocates of the "(bio) psychosocial" school. There is no equal representation of biomedical experts, despite the biomedical nature and complexity of this disease. The fact that virologists, immunologists, endocrinologists, and gastroenterologists are hardly represented in the advisory group says a lot, if not all (Belgische Kamer voor Volksvertegenwoordigers, 2007).

Moreover, the CBT/GET program proposed by the Ministry of Social Affairs and Health is potentially harmful to patients with ME/CFS (Twisk and Maes, 2009). As we have discussed in the latter article, even a slight effort may potentially damage the "health" of many ME/CFS patients. These adverse effects include increased inflammation; incremental dysregulation of the immune system; a further rise in O&NS; decrements in muscle strength; intensification of muscle and joint pain (due to impaired metabolism, lowering of the pain threshold, and central sensitization); increase of neurological impairments (likely caused by blood flow disturbances, hypoxia, metabolic dysregulation, etc.); additional ion channel anomalies and decrement of an already reduced stress response (Twisk and Maes, 2009). Thus, the application of GET as a treatment for ME/CFS – knowing that efforts may be harmful to many patients – should be qualified as bad clinical practice (Twisk and Maes, 2009).

Notwithstanding it was shown by the Belgian Government that CBT/GET has no significant therapeutical effects in the treatment of ME/CFS (Belgian National Heath Care System, 2006) and its potentially harmful effects to patients with ME/CFS (Twisk and Maes, 2009), the National Heath Care System and thus the Ministry of Social Affairs and Health decided to continue the CBT/GET treatments and the financial support to the CFS Reference Centers and even to stress the impact of CBT. Thus, end December 2008, the abovementioned situation deteriorated as can be deduced from the publication of the adapted agreement between the National Health Care System and the CFS Reference Centers (Belgian National Health care System, 2008). In this new agreement it is stated that the main aim of the treatment of CFS patients at the CFS Reference Centers is that patients have to "reflect upon the psychological factors (such as behavior and thoughts) that maintain the complaints and that possibly have caused the condition (functional analysis)". With this new publication, the Belgian Government makes a clear public stand against the fact that ME/CFS is a physical disease. The above shows that the biochemical approach, both in terms of diagnoses and treatments, was definitely eliminated by the Belgian Government to make room for the CBT/GET approach.

Medical Malpractices at the CFS Centers

The Minister's abstention from public stance on the biochemical and immune causes and treatments of "CFS" still allows to earmark ME/CFS patients as hypochondriacs, hysterics, and psychosomatic complainers, although these patients suffer from severe, but often treatable diseases. Still, by public support of the (bio)psychosocial view by the Minister, thousands of patients are treated with nonsense therapies such as methylphenidate, glucocorticoids, botox treatments, repeated operations, nonsteroidal anti-inflammatory drugs, psychoanalytic therapies, morphine pumps, etc. We will discuss now some case reports illustrating cases of medical malpractices, which frequently occur at the CFS Reference Centers.

1. The CFS Center, University Hospital, Antwerp (UZA), Belgium

1.1. A first case report is about a female patient. She was examined and diagnosed by the CFS Reference Center at the University of Antwerp as suffering from CFS. She was prescribed Magnesium and Pregabalin and was advised to follow a GET program. Some days later, this patient was examined in the outpatient Clinics (the Maes Clinics) where the first author of this paper is director, Antwerp, Belgium. There it was detected that this patient had significant abnormalities in the blood tests, e.g. low total carnitine and coenzyme Q10; an IgG3 deficiency; increased IgA levels; increased haptoglobin, orosomucoid and C reactive protein (CRP) levels; increased peroxide concentrations; the presence of serotonin antibodies; and increased IgM and IgA responses against LPS of a number of gram-negative bacteria ["increased" or "lowered" indicates values which are higher and lower, respectively, than the reference values established in the laboratories]. The diagnosis in our clinic was inflammatory fatigue and pain (IFP) (ME/CFS) due to a number of factors, such as low carnitine and CoQ10, inflammation, increased oxidation, autoimmunity (against serotonin) and an increased translocation of gram-negative enterobacteria and, thus, gut-derived-inflammation.

1.2. Another patient consulted the same CFS Center in the context of a follow up. She had fully completed the CBT/GET program and had – according to Reference Center – "acquired sufficient understanding in her health problems". On the occasion of this follow-up, a blood test was carried out by this CFS Center which showed no specific abnormalities. Only a few days later, this patient came to the Maes Clinics, since she felt that she was not treated well at the official CFS Center. First of all, this patient was not only suffering from chronic "fatigue" but also from irritable bowel syndrome (IBS) and major depression, which the internists at this CFS Center were unable to detect. Our biochemical tests showed specific disorders, e.g. signs of T cell activation (increased number and percentage of CD38+ and

HLA-DR+ T cells); low serum acylcarnitine levels; increased C3 and C4 levels (complement factors); increased peroxide levels; high interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNFα) levels; the presence of serotonin antibodies; increased neopterin concentrations; a disturbed lactulose H2 test (suggestive of small intestinal bacterial growth or SIBO) and an impaired fructose test. Our diagnosis based upon our findings was therefore: inflammatory fatigue and pain (IFP) (ME/CFS) syndrome and major depression, in a patient with induction of pro-inflammatory cytokines; auto-immunity against serotonin; and increased oxidation. Moreover, she suffered from SIBO and fructose intolerance, which could explain her symptoms of IBS. But, for the internists of the CFS Reference Center it is more important that patients "gain more psychological insight in their symptoms".

1.3. Another case report is a female patient suffering from gastrointestinal symptoms, "chronic fatigue" and fibromyalgia, secondary to a celiac disease, which was established by biopsy. Following the advice of a private gastroenterologist, she started a gluten free diet and most gastrointestinal and fibromyalgic symptoms subsided within some months. Because the fatigue was not sufficiently improved, she went to the CFS Reference Center of the University of Antwerp. The internist of that Center told her she suffered from "CFS" and not from gluten allergy and, therefore, could stop her diet and should start with CBT. However, it appears that no specific blood tests were carried out to screen for gluten allergy or celiac disease. The patient was very happy to learn that she could stop her gluten diet and started with the CBT sessions. Her symptoms of fatigue, fibromyalgia and the gastrointestinal symptoms, however, increased during the treatment course with CBT. Suddenly, after some months of CBT, the patient got a letter of congratulations from the CFS Reference Center stating that she successfully had completed her treatment and that she had gained good insight in her psychological problems. Because her complaints of "fatigue" and gastrointestinal discomfort had increased during the treatment at the CFS Center this patient came to the Maes Clinics. Biomedical tests showed the following: immune activation with increased numbers of CD38+ T cells; low serum coenzyme Q10; increased serum peroxides; lower serum IgG and gamma globulin levels; increased haptoglobin and C3; increased plasma IL-1β and TNFα levels; increased neopterin levels; presence of serotonin antibody titers; and anti-transglutaminase IgA antibodies. The latter finding indicates celiac disease and the former indicates the presence of an inflammatory response with monocytic and Th1-like activation. We obtained a new gut biopsy and the presence of celiac disease was confirmed. Thus, our diagnosis became: inflammatory fatigue and pain syndrome (IFP) due to celiac disease. Thus, it is clear that because her diet was stopped by the internist of the Antwerp CFS Reference Center, there was a recurrence of the symptoms of celiac disease and therefore of the IFP symptoms. The Maes Clinics immediately restarted the gluten diet and started treatment with specific NAOISs. Doing so, the gastrointestinal symptoms of the patient improved considerably within some months, while also the IFP symptoms improve gradually.

Thus, the CFS Reference Center of the University Hospital Antwerp, makes wrong diagnoses; they do not discover immune activation and inflammatory pathways that are present in patients with ME/CFS, because they fail at using the correct tests; and they do not examine the effects of O&NS, although this phenomenon is known to play a role in the pathophysiology of ME/CFS. Although patients suffer from IBS, SIBO, gastrointestinal symptoms and even celiac disease, the specialists at the CFS Centers do not further examine the gastrointestinal pathways that are involved in ME/CFS or CF due to other organic disorders, let alone that they measure bacterial translocation, another pathway that is involved in ME/CFS (Maes, 2009; Maes and Leunis, 2008; Maes *et al.* 2007a; 2007e; 2008). More important for the CFS Centers is that the patients gain more insight about their psychological problems. After all the CFS Centers are financially supported by the Belgian Government to "treat" the patients with the aim to give them insight in their psychological problems.

2. The Catholic University of Leuven (KUL), Belgium

2.1. Another patient went to the CFS Reference Center of the University of Leuven because she suffered from chronic fatigue and pain and severe gastrointestinal symptoms with the possibility of M.Crohn. This CFS Center could not establish any biochemical abnormalities and no inflammation. The internist of this CFS Center proposed to treat her with Methylphenidate, a treatment which was – fortunately – not followed by the general practitioner of the patient. Moreover, the patient was sent to the psychiatrist, who is a member of the CFS Center and the one of the Belgian godfathers of the "it is all in the mind-school". This professor of psychiatry concluded that they were unable to make the diagnosis of "CFS" because the internal investigations were not complete yet. In any case, they insisted that if the report of the internal investigations were negative, the patient per definition would suffer from "CFS" and that the patient – per definition – should be treated with CBT/GET and absolutely no biomedical treatment might be used. A week later this patient – frustrated by the CFS Reference Center – came to the Maes Clinics. Investigations showed: increased T cell activation markers, such as CD38+, CD38+CD4+, CD38+CD8+ and CD4+HLADR+, and CD8+HLADR+ T cells; increased serum gamma globulin, IgG and IgG2 levels; highly increased immune complexes; low serum carnitine and coenzyme Q10 concentrations; high peroxide levels; low testosterone; elevated blood concentrations of IL-1β and TNFα; increased neopterin concentra-

tions; the presence of serotonin antibody titers; an IgM-mediated immune response against Hafnia Alvei, indicating a loosening of the gut tight junction barrier; increased IgM mediated response to NO2-tyrosine, pointing to increased damage by nitrosative stress; and a lactulose and fructose test, which showed serious problems. Our diagnosis was: inflammatory pain and fatigue (IFP) (ME/CFS) with monocytic and Th1-like activation, autoimmunity (serotonin), oxidative stress and damage by nitrosative stress, and increased translocation of gram-negative bacteria and SIBO.

Thus, this CFS Reference Center made wrong diagnoses – they have not explored the IO&NS abnormalities; and they have not even examined the possible causes of the gastrointestinal symptoms. Another question is why the internists referred the patient to the psychiatrist of the same CFS Center who was unable to make a diagnosis since the investigations were not complete. Even more: the department of psychiatry at this CFS Center has a standardized answer, which proposes the official standardized treatment, i.e. CBT/GET. This CFS Reference Center initiates no treatments at all for the disorders in the IO&NS pathways. Or they propose maltreatments, such as to treat the patients with Methylphenidate, while it is known that this drug may cause more damage caused by O&NS (Martins *et al.* 2006). While the patients suffer from IO&NS disorders, they propose to start treatments with GET, which may cause additional induction of the IO&NS pathways (Twisk and Maes, 2009). While the patients suffer from gastrointestinal symptoms no examinations are carried out and no treatment is advised. Therefore, patients, who are medically ill, are subjected to a long agony, because they are wrongly treated with GET – a treatment that they usually cannot cope with – and CBT – a psychological therapy – that stigmatizes the patients enforcing the idea that all is "in the mind."

2.2. We also would like to stress another case report, which we have published previously. This was a patient with severe ME/CFS due to gut-derived inflammation and, subsequently, autoimmunity, who was labeled as having conversion hysteria and la belle indifference at the University of Leuven, Belgium (Maes *et al.* 2007a). She recovered completely by treating her at the Maes Clinics by means of IVIg and specific NAIOSs (Maes *et al.* 2007a).

In summary, the official CFS Reference Centers do not employ the adequate tests in order to identify the pathways that are involved in ME/CFS. Even worse: based on not recognizing the abovementioned pathways they start therapies, which may further endanger the immune status of the patients (GET) and which do not treat the underlying cause (CBT), thereby deteriorating the condition of the patient (see casus 1.3). The fact that those CFS Centers sent patients with a WHO-established biomedical disorder and with proven IO&ND abnormalities to psychiatrists and physiotherapists for longstanding treatments with CBT/GET is not only unethical and immoral, but also a waste of governmental money. Finally, one can wonder whether the results of patients who "successfully completed their CBT program" – as case report 1.3 – are included in the efficacy outcome statistics as "responders to CBT/GET treatment".

Reluctance of the Belgian Government to employ biological diagnoses and treatments for ME/CFS

The ICD10 and the ICD9-M leave no doubt about the neurological and physical nature of ME/CFS. But, all Belgian public organizations governed by the Ministry of Social Affairs and Health, such as the Superior Health Council and the National Health Care System, consider ME/CFS as a "mental condition". Thus, in fact, the Belgian Government violates the international WHO treaty and ignores the international scientific literature. Thus, in Belgium ME/CFS is considered to be a "psychic" or "psychiatric condition" by the Ministry of Social Affairs and Health and the organizations that it governs.

The above is evidenced by the fact that patients with ME/CFS are frequently denied the prescribed medications, e.g. IVIg. Even if the patient meets the criteria for reimbursement of an IVIg treatment, the National Health Care System often suspends the reimbursement of this expensive treatment to ME/CFS patients. The failure to allow evidence-based treatments, e.g. IVIg for ME/CFS patients with recurrent infections, lowered immunoglobulin levels and (auto)immune responses, while these therapies are allowed and reimbursed to patients with other diagnoses, is not only discriminatory, but also unethical.

The arguments of the Superior Health Council are "the literature review for the treatment of 'CFS' shows that IVIg therapy is not useful", and "there is insufficient evidence for other therapies, e.g. immunological studies on the effectiveness of antibiotics do not allow an unambiguous conclusion." This, of course, is very illogical. Since ME/CFS has multiple trigger and maintaining factors (Maes, 2009), one cannot draw any firm conclusion on a treatment which would be successful to all patients. Indeed, as explained by us (Maes, 2009), the IO&NS pathways that induce ME/CFS symptoms can be triggered by viral and bacterial infections; psychological stress and strenuous exercise. Thus, breakdown of ME/CFS into different subgroups is necessary, since each trigger or maintaining factor asks for a different therapeutical approach. Thus, the induction of the IO&NS pathways following bacterial and viral infections, strenuous exercise or psychological stress demands different therapeutical approaches. Antibiotics are needed for patients with (chronic) bacterial infections (Vermeulen and Scholte, 2006). In ME/CFS patients who

show viral infections, antiviral medications are needed. In this regard, it has been shown that treatment with valacyclovir for six months shows a significant efficacy for ameliorating ME/CFS patients (Lerner *et al.* 2007). Also, subgrouping according to the pathophysiology is needed to pinpoint the most adequate treatment. For example, in ME/CFS patients with common variable hypogammaglobulinemia and IgG subclass deficiencies (an IgG3 subclass deficiency is overrepresented in CFS) and recurrent infections or autoimmunity, IVIg should be administered as a replacement therapy and to normalize the immune disorders (Maes *et al.* 2007a; Kerr *et al.* 2003). In ME/CFS patients with an increased bacterial translocation, specific (NAIOSs), e.g. glutamine and zinc, have a significant clinical efficacy (Maes *et al.* 2008). In subjects with depleted mitochondrial functions, NAIOSs, such as carnitine, have a proven efficacy (Vermeulen and Scholte, 2004; Plioplys and Plioplys, 1997). In patients with fatigue, myalgia and neurocognitive disorders due to a low CoQ10 syndrome, supplementation with CoQ10 can reverse the abovementioned symptoms (Maes *et al.* 2009b).

Improper conduct by the National Health Care System and insurance companies

In this paragraph we will show some examples of malpractices by the Belgian National Health Care System and private insurers, which are made possible by the stance of the Belgian Government which considers ME/CFS as a "psychosocial" disorder.

1. The first case report is a patient in whom CFS and immunological disorders were established by dr. K. de Meirleir. The National Health System decided that this patient could no longer be regarded as incapable to work due to her ME/CFS. The patient had appealed against the decision of the National Health Care System. In its session, the court appointed a psychiatrist-psychotherapist, as an expert. In his report, this psychiatrist decided that this patient was fit to go to work again. This decision was based on his psychiatric examination and on psychological tests. His psychiatric analysis offered neither an adequate description of the internationally accepted criteria of ME/CFS nor any relevant test for this disease. He also reached his verdict using psychological tests, i.e. the Millon Clinical Multiaxial Inventory (MCMI) (Millon, 1977), the coping met pijn vragenlijst (CPV; the coping with pain questionnaire) (Spinhoven *et al.* 1994) and the Rorschach inkblot test (Exner, 2002). The MCMI is a test that aims to examine personality characteristics and it is, thus, not relevant to the physical problems of this patient. The CPV is a pain questionnaire, which scores coping with pain, but not the actual pathology, namely ME/CFS. The use of this test is also irrelevant in patients with ME/CFS. There are several internationally accepted questionnaires that can be used to measure the severity of characteristic ME/CFS complaints e.g. pain, none of which was used by this "expert" appointed by the court. The Rorschach inkblot test dates back from 1921. It is a projective test in which ink spots are interpreted. It is a highly subjective tool with no scientific meaning. The "inter-rater reliability" and the "general validity" are non-existent. Even within the field of psychiatry this test is not valid. So, on the basis of a psychiatric examination, which was carried out inadequately, and by means of irrelevant, not standardized and outdated psychological tests this psychiatrist came to the decision that this patient was fit to go to work. It is ridiculous that the Belgian National Health Care System and the court appoint this kind of psychiatric "experts" to decide about the future of patients suffering from an internationally accepted biomedical disorder. But this is daily practice in Belgium.

2. Another case report. This is a 32-year-old woman who came to consult the Maes Clinics because of "fatigue", and diffuse pains in the muscles, joint pain and morning stiffness. Patient also had serious gastrointestinal complaints. Clinically, the diagnosis CFS, fibromyalgia and IBS could be made but specific blood tests revealed the following: increased gammaglobulins; high serum immune complexes; increased serum IgG and IgA levels; a positive rheumatoid factor and high anti-cyclic citrullinated peptide values; increased oxidized LDL antibodies; increased titers of the antinuclear-factor (with a homogeneous fluorescence pattern characteristic for rheumatoid arthritis (RA) or lupus); increased IgM against pseudomonas aeruginosa; the presence of ganglioside antibodies, namely GM1-IgM and Al-GD1b IgM; and a strongly positive lactulose test. Our diagnosis was inflammatory fatigue and pain secondary to an autoimmune process (RA), increased oxidative stress and increased translocation of gram-negative bacteria; and IBS with SIBO. This patient was enrolled in a private insurance for disability allowance. Notwithstanding our diagnosis – confirmed by an internist – was known to that insurance company, they appointed a psychiatrist as an expert to advise them about "burn-out in the context of a disability policy." This psychiatrist, a University professor, completed a psychiatric examination and he made use of the Minnesota Multiphasic Personality Inventory (MMPI) (Tellegen *et al.* 2003); the Buss-Durkee questionnaire (Buss and Durkee, 1957); the Utrecht coping list (Schreurs *et al.* 1993); and the SCL-90 (Derogatis, 1977) to evaluate the work ability and disability allowance of this patient with fatigue due to an autoimmune process. The MMPI is a personality questionnaire. The Buss-Durkee scores aggressive tendencies. The Utrecht coping list scores coping mechanisms. The SCL-90 scores multiple psychiatric symptom clusters. In no way, this professor gives an adequate description of the internationally accepted criteria of ME/CFS or proper measurements of the real complaints of these patients, namely pain, weakness and exhaustion, although there

are plenty of appropriate questionnaires for fatigue and pain secondary to organic disorders. In his report, he decided that "this patient with a neurotic-hysteric personality with a tendency towards conversion suffered from a somatoform disorder". He reports that within the policy her case should be regarded as "a nervous or mental disorder" and that "no objective signs are present which makes the diagnosis of an organic disorder indisputable". Above all, his report on axis-3 of the DSM-IV diagnostic system (the axis where the relevant organic diseases should be given) stated that "no objective organic disorder is present". Phrased differently, he declares that no organic disease is present, while he knew all results of the immune blood tests and although he did not perform any organic examinations. This also is daily practice in Belgium.

Thus, university professors, civil servants, in Belgium offer a service to insurance companies by which they are paid by stating that patients do not suffer from an "biomedical disease", but rather from a psychiatric illness. The Belgian National Health Care System and private insurance companies make use of the fact that "CFS" is declared to be a "mental condition". They use this argument to refuse the disability allowance, which the patients are entitled to receive, on the basis of exclusion of mental disorders listed in the policy. Arguably the main reason why the Belgian Government views ME/CFS as a mental condition is a financial one: patients with a mental condition can easily be banned from the National Health Care and withdrawn from disability allowances, which in Belgium are paid by private insurers and/or the National Health Care System.

Witch hunt by the Ministry of Social Affairs and Health?

The public stance of the Minister of Health that ME/CFS is "a mental condition" and may not be treated medically causes not only great harm – both medically and financially – to the tens of thousands of patients with ME/CFS, but apparently this erroneous point of view is also a license to prosecute physicians and scientists who deal with the biochemical causes of ME/CFS. Some examples – that happened to various physicians who treat and examine ME/CFS patients medically – are in place.

1. Ethical committees which are under the guardianship of the Ministry of Social Affairs and Health

It is not uncommon that new study projects about the immune pathophysiology of CFS submitted for approval by the local ethical committees are rejected because the members of the ethical committees judge that the subject, i.e. ME/CFS is irrelevant, unless it is a project that is put forward by the CFS Reference Centers. The ethical committees are also under the jurisdiction of the Minister of Social Affairs and Health. As an example: one of the research projects of the first author of this paper on the biochemical causes of ME/CFS was submitted to the ethical committee of the AZ KLINA, a hospital in Antwerp, Belgium. The aim was to examine the pathways underlying the gut-derived inflammation, which were detected in ME/CFS (Maes *et al.* 2007a; 2008). Indeed, we published that ME/CFS is accompanied by increased IgM and IgA responses to the LPS of gram-negative bacteria, indicating loosened tight junctions of the gut or leaky gut, which has caused bacterial translocation. Once the LPS of the gram negative bacteria reaches the blood, an IgA- and IgM-mediated immune response may be mounted. As we reviewed previously, this phenomenon can induce the IO&NS pathways, which in turn can cause specific symptoms of ME/CFS (Maes, 2009). Normalization of this pathway by specific NAIOSs, such as glutamine and zinc, is accompanied by a clinical improvement or remission in many patients, showing that increased bacterial translocation plays a role in the pathophysiology of ME/CFS (Maes *et al.* 2008). Therefore, our new project aimed to examine the causes of increased gut permeability, e.g. by measuring alterations in zonulin, which regulates the function of the tight junctions (Fasano *et al.* 2000). This project was co-created by a collaboration of different international universities and research institutes, some of which the most prestigious in the world. The psychiatrist of this local advisory board has never published a peer-reviewed paper, let alone an article on ME/CFS. But within this Institutional Review Board he – as the only psychiatrist – has most power to influence the decision to be taken, since ME/CFS is considered to be a mental condition. The outcome of the Review Board's decision was as expected. They decided that this project was irrelevant; that the researchers were inadequate, i.e. the first author of this paper (a ISI highly cited author) and top international groups; that the institutions where the research was to be carried out, i.e. some top laboratories and research institutes all over the world, were incompetent; and ultimately that the project can not be performed. Doing so, the Belgian Government obstructs important biomedical research on ME/CFS.

2. The Belgian National Health Care System under the jurisdiction of the Ministry of Social Affairs and Health

The National Health Care System even pursues physicians involved in the immunological treatment of ME/CFS. A good example here is the treatment with IVIg. It has been shown previously that this treatment in useful in some patients with ME/CFS, e.g. those with lowered IgG3 levels, repeated infections, (auto)immune disorders and leaky gut (Maes *et al.* 2007a). As discussed above, patients who are treated with IVIg because they suffer from repeated infections and have lowered IgG

levels, are reimbursed by the National Health Care system, unless they are known to suffer from ME/CFS. Internists who had treated ME/CFS patients with IVIg are being prosecuted by the National Health Care System because they have prescribed IVIg, which according to the physicians of the National Health Care System cannot be reimbursed. Consequently, these treating physicians are pursued to compensate for all costs made by the National Health Care System for the IVIg treatment. This means that these physicians have to pay back several hundred thousand of euro's to the National Health Care System.

3. The Medical Board under the jurisdiction of the Ministry of Social Affairs and Health

Also the Medical Board seems to be mobilized to prosecute physicians who are involved with the medical diagnoses and treatments of ME/CFS. The Medical Board in Belgium is not comparable to it counterparts in other countries. During an official investigation the Medical Board requires that the defendant has the duty to cooperate with the investigation and may not remain silent nor conceal certain facts. In other words, the Medical Board requires self-incrimination. The magistrate who is present as an assessor at the councils to protect the rights of the defense has a consultative voice to the complaints on disciplinary rules, but he can also appeal against a ruling. This means that at the same time he is both judge and party. Moreover, it happens that the above magistrate infringes the right of defense by intimidations and that during the procedures other members of the Board forge, deliberately writing false information in their reports. During the course of justice, it is impossible to call witnesses, either "a charge" or "a discharge". In the past, Belgium was already condemned by the European Court of Human Rights (ECHR) for violation of the fundamental right to a public hearing, since the whole process in the Board took place behind closed doors. That policy was not fundamentally changed after the conviction by the ECHR. A new lawsuit against the Board will be brought forward for the ECHR by one of the most successful plastic surgeons in Belgium. He was convicted by the Board because he affected "the honor and the dignity" of the medical profession. Although not one rule stipulates what "honor and dignity" stands for, the local Boards regularly use that kind of convictions to eliminate physicians and private clinics that are too successful. Thus, during their investigations, the Medical Board constantly breaches the rights of the defense, e.g. ECHR article (art) 6, i.e. articles 6.1, 6.2 and 6.3 and the International Covenant on Civil and Political Rights (ICCPR), articles 14, i.e. 14.1, 14.2, 14.3 paragraph b, c, d, e, and g. Physicians who refuse to pay the yearly contribution to the Medical Board, because they criticize the Medical Board to be undemocratic, can be thrown into jail and face seizure of their goods.

Most important, the existing disciplinary laws of the Medical Board are not suitable to monitor the quality of the medical practices. The disciplinary councils in the different Belgian regions (provinces) have their own private rulings, which are not published systematically creating a lack of openness; one cannot draw the right lessons about which ruling is actually applied. All previous efforts to correct the undemocratic nature of the Belgian Board and to change the disciplinary rules into more efficient rules, i.e. rules that really are able to monitor the quality of medicine, did not succeed (e.g. in 1987, the Minister of Social Affairs De Haene). Therefore, in a recent symposium ("The Belgian Medical Board: Undemocratic and Unconstitutional") the consensus between physicians and politicians was that the Medical Board as it now stands should be changed radically (Maes *et al.* 2009a).

One method of the Medical Board to enforce their refutable standpoints is to prosecute physicians because they have prescribed too many so-called unnecessary blood tests, e.g. indicators of the IO&NS pathways. This is ruled to be an "offense" or "medical overconsumption" and it is sanctioned with a warning or a suspension of several days to weeks. This approach can be explained since the specialism "psychoneuroimmunology" is regarded in the Benelux countries as the "parapsychology of the 21st century".

Moreover, the Medical Board shows an abstention from public stance on the biochemical causes of ME/CFS, which can be illustrated by the absence from the international symposium in Antwerp, Belgium 2007, 3th of May, despite repeated invitations by the first author of this paper. On the other hand, official complaints made against the abovementioned malpractices at the CFS Reference Centers and the psychiatrists/physicians who function as ME/CFS experts for the National Health Care System or private insurances, are not brought forward in their courts. As a consequence, the Medical Board – as "self-declared guardians of a high quality medicine" – allow medical errors on a large scale and allow the suffering of the ME/CFS patients to continue.

4. Collusions

Principal members of the Medical Board are well-known opponents of the biochemical approach of ME/CFS and participate in the University CFS Reference Centers. An example is the Medical Board of the province Antwerp. The only professor of psychiatry within this Medical Board, Antwerp, is ex-President of this Board; member of the National Medical Board; and he participated in the CFS Reference Center of the University of Antwerp, where he was Chairman of the Department of Psychiatry (until 2009). He is frequently invited to function as an expert for the evaluation of ME/CFS patients. This record shows that he is assumed to be the expert and the most prominent figure of the Board

especially when problems occur within the discipline of psychiatry and, thus, "CFS". When he is appointed as expert to evaluate ME/CFS patients, he uses a comprehensive psychological test battery to "resolve the issue" and to "psychologize" this biomedical disorder. He does not employ the state-of-the-art biochemical tests to diagnose ME/CFS. Moreover, this professor committed infringements against the good publication practice and thus committed intellectual dishonesty during his career, because he demanded from his assistants to be the first author on articles which he has not contributed to (Cosyns *et al.* 1989) or to be co-author to papers he did not contribute to (examples are: Maes *et al.* 1989a; 1989b). Thus, this professor has built his scientific curriculum vitae on the basis of someone else's work after he acquired an appointment as a professor even without having published peer-reviewed papers. This kind of judges is used by the Belgian Government to rule and to judge to decide what high-quality medicine is and to ensure the quality of medicine with regard to ME/CFS.

To ascertain that physicians are restricted to treat "CFS" by the official approach, i.e. CBT/GET, the Medical Board even go so far to condemn international specialists for their scientific inventions which are published in international journals and their clinical use of the established biochemical diagnoses and treatments of ME/CFS. This also happened to, amongst others, the Maes Clinics, Antwerp, which is located 5 km from the official CFS Reference Center at the University of Antwerp.

1) The Medical Board declared that the Maes Clinics made an offense because they employed a test that is not suited to measure leaky gut in CFS. Indeed, the Medical Board states that leaky gut should be diagnosed by the "lactose-manitol test" and not through the assay of IgM and IgA responses directed towards LPS of gram-negative bacteria (Maes *et al.* 2007a; 2007e; 2008). In their scientific ignorance they even use "lactose-manitol" instead of the correct term "lactulose-mannitol" test. The latter test is commonly used to measure leaky gut, but Maes *et al.* detected that many more subjects with ME/CFS suffer from an IgM and/or IgA mediated immune response against bacterial LPS than from a disturbed lactulose-mannitol test.

2) The Medical Board declared that the Maes Clinics made an offense, because they treat patients with ME/CFS and leaky gut. This apparently is a violation because – as the Medical Board states – leaky gut is an internal problem and should be treated by the experts of a multidisciplinary team. As Maes *et al.* (2007a; 2007e; 2008) were the first to demonstrate that increased bacterial translocation is a new pathway in ME/CFS, it is not entirely clear who these experts could be, but probably the Medical Board refers toward the CFS Reference Centers. The latter are – as explained above – not able to detect SIBO and gluten intolerance with coeliac disease, let alone leaky gut or an increased translocation of gram-negative bacteria.

3) The Medical Board declared that the Maes Clinics made an offense, because they use biochemical tests that quantify the IO&NS abnormalities. Thus, it appears that the use of these tests in patient populations has become punishable in Belgium. After all, the Belgian Government decided that using biochemical tests for ME/CFS is not "in accordance with a high-quality medicine." They do not consider the reports on the use and the significance of these tests for the etiology and pathophysiology of ME/CFS, although all those tests are discussed extensively in international journals (Maes, 2009; Maes *et al.* 2005; 2006a; 2006b; 2007a; 2007b; 2007c; 2007d; 2007e; 2008; 2008; 2009b; Mihaylova *et al.* 2007; Lorusso *et al.* 2009; Spence *et al.* 2008; Buchwald *et al.* 1997; Vermeulen and Scholte, 2004; Vecchiet *et al.* 2003; Kennedy *et al.* 2005; Smirnova and Pall, 2003; Jammes *et al.* 2005).

4) The Medical Board declared that the Maes Clinics made an offense, because they treat patients with what they call "expensive treatments". The Medical Board does not take into account that these biochemical treatments are much less expensive for the National Health Care System than the useless and harmful, long-term treatment with CBT/GET. Moreover, the biochemical treatments have a significant clinical efficacy in treating CFS, are evidence-based as they are based on biochemical assays and based on the scientific literature as discussed above (Lerner *et al.* 2007; Endresen, 2003; Maes *et al.* 2007a; 2008; Vermeulen en Scholte, 2004; 2006; Plioplys and Plioplys, 1997). But the Medical Board follows the statements of the Ministry of Social Affairs and Health that "biochemical treatments for CFS" are not "in accordance with a high-quality medicine".

5) On top of that, the Medical Board invents new allegations. The Medical Board declared that the Maes Clinics made an offense, because the Clinics would require that all their patients undergo HIV testing. Although some physicians would argue that in adult patients with ME/CFS it is wise to carry out HIV testing, figures show that in the Maes Clinics only 11 HIV tests were carried out on a total of 1442 blood tests and this only on the request of the patient.

By pursuing the abovementioned internists, psychiatrists and general practitioners the Medical Board and the Belgian Government infringe the Belgian civil laws (case Dr Thierry Hertoghe, June 5, 2006), which establish that the Medical Board is not in the position of judging the scientific nature of treatments. The Medical Board and thus the Ministry act unethical because they infringe article 36 of the medical code, i.e. that the physician has the diagnostic and therapeutic freedom. The abovementioned illustrates that the Ministry employs the Medical Board and some of its members to abate the

competing biologically-oriented physicians and clinics, which have a higher success rate than the official CFS Reference Centers in treating ME/CFS.

Conclusions

Using public organizations to enforce the "(bio) psychosocial" approach, the Ministry of Social Affairs and Health and the National Health Care System abstain tens of thousands of patients from a proper diagnosis and treatment and impose their will on the Belgian population, ME/CFS patients and physicians treating ME/CFS. They monopolize CBT/GET as the only "useful treatment" for ME/CFS, this while they themselves have proven that these treatments have no clinical efficacy and while these treatments are harmful to the patients.

While thousands of studies have demonstrated physical abnormalities, while numerous studies have shown specific biological treatments to be effective for specific subgroups of ME/CFS patients, and while research and clinical practice have proven the "(bio)psychosocial" approach to be ineffective and, in many cases, even harmful (Twisk and Maes, 2009), the Belgian government enforces their unjust CBT/GET policy.

Internationally recognized scientists and physicians who work biochemically, and are therefore not connected to the CFS Reference Centers, not only receive no financial support for their research endeavors, but they are also silenced and ultimately prosecuted.

With regard to ME/CFS, Belgium seems to have returned to a medieval situation, in which the Ministry of Social Affairs and Health, prosecutes researchers and physicians employing successful treatment methods, because the medical approach is not compatible with the useless and harmful CBT/GET strategy that the Ministry has coined some years ago. This situation resembles what happened to Galileo Galilei in the 17th century.

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