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Antioxidant Treatment of Chronic Fatigue Syndrome

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ABSTRACT: In a randomized, double-blind, crossed-over study, 22 patients with chronic fatigue syndrome were treated for 3 months with an extract of pollen. A statistically significant improvement was noted for total well-being and for the following 7 relevant clinical symptoms: fatigue, fatigability, sleep problems, depression, intestinal problems, cold hands and feet, and hypersensitivity to smoke and odors. Estimation of erythrocyte fragility, a possible indicator of oxygen free-radical damage, demonstrated a highly significant improvement. Since the pollen extract used in this study is known to be a strong antioxidant, it is speculated that symptoms in chronic fatigue syndrome may be mediated via free radicals. Treatment with antioxidants may now be considered in cases of chronic fatigue syndrome, since effective treatment has largely been lacking. Further studies are necessary to find optimal dosage and long-term effect, as well as optimal preparation or combination of preparations to be used. (*Clinical Practice of Alternative Medicine* 1(2):88-91, 2000)

In surveys on chronic fatigue syndrome (CFS), it is generally stated that no effective treatment exists that improves the situation for the patient.¹ However, patients with CFS often state that antioxidants have a positive effect. Also, using a method for the assay of erythrocyte fragility, a tendency to parallelism between such fragility and symptoms can be found. These findings formed the basis for this study, involving treatment with a broad-spectrum antioxidant preparation known to positively influence properties of erythrocytes, and involving analysis of relevant symptoms as well as erythrocyte fragility.

Methods and Materials**Patients**

Twenty-two patients were included in the study, 3 men and 19 women, ages 27 to 70, with a mean age of 50 years. One woman moved after 1 treatment period and discontinued her participation. All other patients completed the study, which provided results from 21 periods of 3-month treatments with active substance and 22 periods of 3-month treatments with placebo. Results are also given from a pilot study of dose effect in 80 patients, including 20 from the double-blind study, in which the dose was 6 times higher.

Design

This study was randomized, double-blind, and crossed-over. All patients were given active substance or placebo for 3 months, then no treatment for 2 weeks (wash-out period), and then active substance or placebo for another 3 months. With this design, 5 patients had placebo during the first treatment period of 3 months and active substance during the second; 5 patients had the active preparation during the first treatment period

of 3 months and placebo during the second period; 6 patients had placebo during both periods; and 6 patients had the active preparation during both periods. An independent pharmacologist made the randomization and neither the patients nor the operator knew what had been given until all figures for all assays had been transferred to the pharmacologist. One period denotes treatment for 3 months, either by pollen extract or placebo.

Diagnosis and Criteria for Inclusion or Exclusion

Diagnosis was made according to criteria given by an international group of experts; these criteria included severe fatigue, decreasing capacity for work by more than 50%, and duration more than 6 months.² Other criteria for inclusion included age between 18 and 70 and a symptom score of 49 or more for 13 symptoms and 5 or more for total well-being (to include only relatively serious cases). Criteria for exclusion were smoking, active dental treatment, electrical hypersensitivity, pollen allergy, other diseases of importance, age under 20 or over 70, use of drugs or antioxidants, and other medical treatment.

Analyses

Subjective symptoms were estimated by the patient on a scale from 0 to 10, in which 0 indicated no problem and 10 indicated an extremely serious symptom. The subjects were evaluated at outset and at 1, 2, 3, 3.5, 4.5, 5.5, and 6.5 months. Figures are only presented for the start and end of each 3-month treatment period.

The following 14 symptoms were estimated: total well-being, fatigue, fatigability (ie, the need for rest after physical exhaustion), sleep problems, depression, intestinal problems, cold hands and/or feet, hypersensitivity for smoke and odors, memory and/or

concentration difficulties, hypersensitivity for light and/or sound, headache, muscular pain, tendency toward infections or feeling of infection, and other symptoms not included here that are commonly noted in CFS.

Free-radical activity was measured as erythrocyte fragility (degree of damage to red blood cells). One drop of capillary blood was taken onto a glass slide as 5 small, thin drops. After drying horizontally, the slide was analyzed at low magnification in the microscope and the number of hemolyzed red cells was estimated by the degree of presence of white, empty lacunae on a scale from 0 to 10 (0 = no lacunae; 10 = lacunae all over the drop). The scale for 5 drops went from 0 to 50. This method has been described in more detail in the literature.^{3,5}

The patients were also asked to evaluate the quality of the medical care they had experienced before the start of the study. Patients reported how they had been received on a scale from 0 to 10 (10 = always well received; 0 = always badly received) and how satisfied they were with the effect of their medical treatment (10 = always perfect care; 0 = always ineffective care or no care). The same scale was also used for an estimation of the treatment patients had obtained at the social insurance office. Statistical analyses were performed using the Student *t* test.

Treatment

The treatment consisted of pollen and pistil extract or placebo, 7 tablets per day, taken in 1 dose at breakfast. This dosage was chosen because a similar dosage, 6 tablets per day, has been shown to have an antioxidative effect.⁶ The preparation used in this study (Polbax) has a unique composition, method of production, source, and high superoxide dismutase-like activity. The source is freshly harvested pollen grains and pistils from the family *Gramineae* spp. The pollen grains and the pistils are collected separately by machines specifically designed for this purpose. After collection, pollen grains and pistils are thoroughly analyzed for purity and specificity. The free-radical scavenging base material is produced in a reactor, in which pollen grains and pistils are allowed to react under specific conditions. The reactant solution is partly evaporated to concentrate the solution and to increase the activity. This product contains superoxide dismutase-like activity, probably antioxidants of type polyphenols.⁶ Polbax is a registered natural preparation at the Swedish National Medical Products Agency; placebo was made according to the rules given by this agency.

Side-Effects

There were no clear side-effects noted during the study, with the exception of slight intestinal inconvenience for a few days in 1 or 2 patients.

Results

A significant decrease of symptoms was noted during active treatment compared to placebo. Numbers are shown only for the start and after the end of the 3-month treatment (Table 1) for general well-being and for 7 of the relevant symptoms: fatigue, fatigability, sleep problems, depression, intestinal problems, cold hands and/or feet, and hypersensitivity to odors. In the placebo group, there was a slightly significant improvement of memory and concentration. The following 5 symptoms did not change significantly in any of the 2 groups: light and/or sound hypersensitivity, headache, muscular pain, tendency to or a feeling of infections, and other symptoms.

In the pollen extract treatment periods, a highly significant decrease of the free-radical activity, as measured by the erythrocyte fragility test, was found (Table 1). There was no significant change in the placebo group.

When the dose was increased 6 times in an open study of 80 patients, an even more marked improvement of general well-being was noted after only 1 month of treatment ($P < .001$).^{3,4}

In the group treated with the pollen extract, an improvement of total well-being was found in 13 of 21 3-month treatment periods, no change was found in 6 of 21 3-month periods, and a decrease was found in 2 of 21 3-month periods (Table 2). The corresponding figures for the placebo periods were improvement in 5 of 22, no change in 13 of 22, and a decrease in 4 of 22 (Table 2). The patients' estimation of the quality of the medical care clearly mirrors the lack of effective medical treatment and how this fact makes the patients also complain about insufficient behavior (real or only in the eyes of the patients) from the medical staff (Table 3).

Discussion

In surveys on CFS, it is generally stated that the cause of this disease is unknown and that there is no effective treatment.^{1,2} Also, adaptation to the decrease in ability is usually stated to be of great importance, ie, the patient must avoid trying to do too much. This is often difficult for the patients to learn, since, in most cases, they are ambitious and cannot accept their handicap. Pressure from uncomprehending relatives, friends, and colleagues, who do not understand that this disease is real, tends to make the necessary adaptation even more difficult.

Although there is a general consensus that no effective treatment exists, this is not quite true. A positive effect of treatment has earlier been published for essential fatty acids⁷ and, recently, for nicotinamide adenine dinucleotide, reduced form.⁸ Also, a deficiency of vitamin B₁₂ in the central nervous system has been demonstrated and may motivate treatment.⁹

TABLE 1
Mean values for estimated symptom score and erythrocyte fragility before and after 3 months of treatment

Symptom	Active	<i>P</i>	Placebo	<i>P</i>
Total well-being	7.14 – 5.48	<.01	6.66 – 6.45	NS
Fatigue	7.95 – 7.52	<.05	7.32 – 7.14	NS
Fatigability	6.90 – 6.60	<.05	7.59 – 7.45	NS
Sleep problems	6.56 – 6.32	<.01	7.42 – 7.33	NS
Depression	5.90 – 5.16	<.001	6.70 – 6.60	NS
Intestinal problems	4.52 – 3.95	<.05	4.14 – 3.86	NS
Cold hands and/or feet	3.87 – 3.61	<.05	3.91 – 3.81	NS
Odor sensitivity	4.21 – 3.69	<.01	4.07 – 4.03	NS
Erythrocyte fragility (free radicals)	19.5 – 17.3	<.001	20.8 – 21.2	NS

NS indicates not significant. Six other symptoms—memory and/or concentration difficulty (slightly improved in the placebo group, $P < .05$), sound and/or light sensitivity, headache, muscular pain, tendency toward infections, and other common symptoms in CFS—were not significant in both groups.

TABLE 2
Number of patients who reported a change in total well-being

Change	Active treatment n=21	Placebo n=22
Worse	2	4
No change	6	13
Better	13	5

The positive effect of the pollen extract used in this study adds to the motive to treat the disease actively. The preparation has earlier been demonstrated to have a strong antioxidant effect⁶; therefore, the positive effect might be mediated via a protective effect against free radicals. The findings in this study of a decrease in erythrocyte fragility further indicate this possibility.

It is not clear what the assay of erythrocyte fragility, used in this study, actually measures. Oxygen free radicals cause lipid peroxidation in living cells, including erythrocytes.⁶ This damage is known to cause polymerization of membrane components, reduced deformability,⁶ and a

TABLE 3
Quality of the medical care and care from the social insurance office, estimated by 22 patients on a scale from 0 (very bad treatment or care or no help at all) to 10 (always very good treatment, care, and help).

Estimation	Treatment	Care	Social insurance
0-4	7/22 = 31.8%	17/22 = 77.3%	9/22 = 40.9%
5-10	15/22 = 68.2%	5/22 = 22.7%	13/22 = 59.1%

tendency to hemolysis. These changes may, induced by free radicals, cause the changes noted in the erythrocyte fragility test.

Because the patients' well-being was improved but not cured, further studies are needed to find the optimal dosage, as well as long-term effects. Such studies have already started, and preliminary results tend to demonstrate a much stronger effect of a much higher dose.^{3,4} Because a combination of many antioxidants tends to give synergy effects, the effects of treatment with a combination of many different antioxidants would also be worth study.

The answers given to the questions concerning the quality of the care demonstrate a deficiency in care. This is not surprising, considering the lack of effective treatment. More remarkable may be the fact that the patients were dissatisfied with how they were received by the doctors and nurses and at the social insurance offices. The medical staff may tend to react as laymen and not fully accept that the patient has a general illness. Possibly, this reaction is often caused by frustration at not being able to help effectively. Also, for the same reason, the lack of effective treatment, the patients may

think that they are less well received by the medical staff than they actually are.

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