# Chronic Fatigue Syndrome

## *Do herbs or homeopathy help?*

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SUMMARY

**To determine the effect of certain herbal and homeopathic preparations on symptoms, lymphocyte markers, and cytotoxic function of the lymphocytes in patients with chronic fatigue syndrome, we studied six outpatients diagnosed with the disease by their family physicians. Patients were given herbal and homeopathic preparations after a 3-week symptom-recording period. After treatment, symptoms were again recorded. Blood samples were taken before and after treatment. None of the values showed any significant change after treatment.**

RÉSUMÉ

**Afin de déterminer les effets de certaines plantes médicinales et préparations homéopathiques sur les symptômes, les marqueurs des lymphocytes et la fonction cytotoxique des lympocytes chez les patients atteints du syndrome de fatigue chronique, nous avons étudié six patients non hospitalisés chez qui leurs médecins de famille avaient posé ce diagnostic. Après trois semaines de cueillette de données concernant leurs symptômes, on a distribué aux patients des plantes médicinales et des préparations homéopathiques. A la fin du traitement, on a procédé à une nouvelle cueillette de données concernant les symptômes. Des prélèvements sanguins ont été effectués avant et après le traitement. Les valeurs obtenues n'ont permis de constater aucun changement significatif après le traitement.**

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CHRONIC FATIGUE SYNDROME (CFS), also known as chronic Epstein-Barr syndrome, "yuppie flu," myalgic encephalomyelitis, and Royal Free disease, is a poorly understood symptom complex characterized by chronic debilitating fatigue, recurrent flulike symptoms, enlarged lymph glands, and several other symptoms, often with no laboratory evidence of abnormalities.[1,2] Diagnosis is difficult. The disease is often cyclical, with exacerbations and remissions, making treatment and the evaluation of efficacy complicated. The fatigue of CFS is so severe that patients are often unable to get out of bed, often cannot work, and may become very depressed by the length of time the condition lasts.

When orthodox approaches fail to alleviate the condition, patients often seek alternative forms of health care, including naturopathy, homeopathy, and other "natural healings." Many herbal mixtures, homeopathic remedies, immune modulators, and other natural supplements have been suggested to help the problem, but little evidence supports their efficacy. A recent supplement to *Reviews in Infectious Disease* is entirely devoted to various aspects of CFS, from the possible viral etiology[3-5] and clinical presentation[6] to considerations important for designing studies comparing CFS patients with normal or "exposure" controls.[7]

This paper examines the effect of two herbal preparations, a homeopathic remedy, and an amino acid on the condition of six CFS patients. The remedies for this study were chosen as a result of enthusiastic testimony from a patient that this combination of remedies had cured her sister "almost immediately." The purveyor of these remedies, a naturopathic physician, was contacted and confirmed that, in her experience, they were indeed powerful and that many of her patients were responding well in a short time.

In an attempt to document objective evidence of change, a number of immune parameters were studied both before and after treatment. Several papers have documented evidence of immune system changes in CFS, such as T cell dysfunction,[8,9] functional deficiency of natural killer (NK) cells,[10,11] a decrease in CD3 expression,[12] and an elevation in CD56+ cells.[10,11,13,14] These parameters were monitored in our study. In addition, patients carefully monitored their own symptoms for 6 weeks.

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## METHODS

Six patients (five women and one man) diagnosed with chronic fatigue syndrome

*Table 1.* **CHRONIC FATIGUE AND IMMUNE DEFICIENCY SYNDROME QUESTIONNAIRE:**
*Minimum score is 28.*

| CRITERIA | ASSIGNED POINTS | PATIENT POINTS |
|---|---|---|
| **Major** | | |
| **1.** Persistent or relapsing debilitating fatigue with no previous symptoms that does not resolve with bed rest and is severe enough to reduce average daily activity to below 50% of normal for six months | 10 | ____ |
| **2.** Exclusion, by history, physical examination, and appropriate laboratory investigation, of other medical conditions that would account for the symptoms and signs | 10 | ____ |
| **Minor** | | |
| **1. Symptoms** | | |
| (a) Mild fever (37.5°C-38.6°C) | 1 | ____ |
| (b) Intermittent sore throat | 1 | ____ |
| (c) Painful glands in neck or armpit | 1 | ____ |
| (d) Generalized muscle weakness | 1 | ____ |
| (e) Muscle aches or pains in several places | 1 | ____ |
| (f) Fatigue for 24 hours or more after exercise | 1 | ____ |
| (g) Generalized headaches | 1 | ____ |
| (h) Joint pain that moves from one place to another | 1 | ____ |
| (i) One or more of the following: dislike of light, forgetfulness, irritability, confusion, difficulty thinking, inability to concentrate, depression (score total no more than one) | 1 | ____ |
| (j) Change in sleep pattern (increase or decrease) | 1 | ____ |
| (k) Initial symptoms developed over several hours or days | 1 | ____ |
| **2. Physical criteria** (physician evaluated) | | |
| (a) Low-grade fever (37.6°C - 38.6°C) | 1 | ____ |
| (b) Nonexudative pharyngitis | 1 | ____ |
| (c) Palpable, tender axillary or cervical lymph nodes | 1 | ____ |
| **TOTAL** | **34** | |

*Modified from diagnostic criteria of Holmes et al.*[15]

entered the study voluntarily, by referral from the local Kingston CFS support group. Each of the subjects gave written informed consent. We obtained Queen's University Ethics approval for in vitro studies on natural and lymphokine-activated killer (LAK) cells in humans. The herbal remedies used are common in a holistic practice.

Duration of the syndrome ranged from 6 to 9 years, and the average age of patients at entry was 48.3 years. To support the diagnosis, patients received a questionnaire derived from criteria proposed by Holmes et al.[15] We developed this questionnaire by assigning 10 points for major criteria and one point for each of the minor criteria proposed by Holmes et al. Point assignment was arbitrary, and the questionnaire has not been subjected to specificity and sensitivity testing. Each patient had to score at least 28 to support the diagnosis and continue in the study. All initial volunteers fulfilled this criterion (*Table 1*[15]).

Each subject was asked to record, on a scale of 0 to 10, 18 of the minor criteria symptoms suggested by Holmes et al,[15] daily, for 3 weeks, before treatment. At the end of this time, blood was drawn for the following hematologic and immunologic parameters: complete blood cell count, differential, lymphocyte markers CD3, CD16, and CD56, NK activity against K562, and LAK cell activity against RAJI (an Epstein-Barr virus – positive, Burkitt's lymphoma cell line).[16,17] The cytotoxic cell assays were 18-hour chromium-51 release assays using purified lymphocytes. Cytotoxicity was expressed relative to well characterized normal donor controls using lytic unit values.[18] In some patients, Public Health Service Laboratories determined antibody titers against Epstein Barr virus EA (early antigen) and VCA (viral capsid antigen).

The treatment phase consisted of the self-administration of two herbal tinctures, one amino acid, and one homeopathic remedy, as follows: Echinaceae Herbal – 15 drops twice daily for 3 weeks,[19,20] Minor Bupleurum – 15 drops twice daily for 3 weeks,[21] Lysine Herbal – 2 capsules twice daily for 3 weeks (Zand Herbal Products), and Gelsemium 30X – 10 drops three times daily for 1 week (Dolisos Corp, Canada).[22]

Echinacea Herbal is a tincture of *Echinacea angustifolia* in an herbal-alcohol base, and is anecdotally reported to be "the most effective blood and lymphatic cleanser in the botanic kingdom, and an immune system stimulant."[20] It is used mainly for bacterial and viral infections.[19,20] Minor Bupleurum, known as Hare's Ear Root in English,[21] is a tincture of *Radix bupleuri* in an alcohol-herbal base, and is used for alternating chills and fever, dizziness, vertigo, bloating, and indigestion. Lysine Herbal, the amino acid lysine (500 mg) encapsulated in an herbal base, is described as being antiviral in the recommended dose, and has been used as a preventive for persistent oral herpes infections.[21] Gelsemium 30X is a homeopathic remedy.[22]

At the end of the 3-week treatment period, blood was again drawn for analysis

*Table 2.* **MEAN SCORES FOR INDIVIDUAL SYMPTOMS BEFORE AND AFTER TREATMENT.**

| SYMPTOM | Pretreatment Means (N = 6) | Post-treatment Means (N = 6) | Pretreatment Category | Post-treatment Category |
|---|---|---|---|---|
| Debilitating fatigue | 5.9 | 6.0 | Severe | Severe |
| Fever | 3.0 | 2.5 | Moderate | Moderate |
| Sore throat | 3.5 | 3.9 | Moderate | Moderate |
| Painful glands | 3.6 | 3.3 | Moderate | Moderate |
| Muscle weakness | 4.8 | 5.2 | Moderate | Severe |
| Muscle aches | 5.1 | 4.9 | Severe | Moderate |
| Postexercise fatigue | 5.8 | 6.3 | Severe | Severe |
| Headaches | 2.4 | 2.8 | Mild | Mild |
| Joint pain | 4.8 | 4.4 | Moderate | Moderate |
| Photophobia | 4.1 | 3.3 | Moderate | Moderate |
| Forgetfulness | 4.5 | 4.1 | Moderate | Moderate |
| Irritability | 3.8 | 3.7 | Moderate | Moderate |
| Confusion | 3.6 | 3.7 | Moderate | Moderate |
| Difficulty thinking | 4.1 | 3.9 | Moderate | Moderate |
| Hard to concentrate | 4.2 | 4.6 | Moderate | Moderate |
| Numbness or tingling | 3.5 | 4.9 | Moderate | Moderate |

*Table 3.* **HEMOGLOBIN, WHITE BLOOD CELL COUNT, AND DIFFERENTIAL BEFORE AND AFTER TREATMENT.**

| CASE | TIME | HEMOGLOBIN (G/L) | WHITE BLOOD CELLS ($10^9$/L) | NEUTROPHILS (%) | LYMPHOCYTES (%) | MONOCYTES (%) | EOSINOPHILS (%) | BASOPHILS (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Pretreatment | 136 | 15.1 | 72 | 21 | 03 | 02 | 01 |
| | Post-treatment | | 10.3 | 64 | 24 | 02 | 09 | 01 |
| 2 | Pretreatment | 150 | 5.3 | 48 | 46 | 02 | 04 | 00 |
| | Post-treatment | | 7.1 | 68 | 31 | 01 | 00 | 00 |
| 3 | Pretreatment | 128 | 6.0 | 63 | 32 | 03 | 02 | 00 |
| | Post-treatment | | 6.7 | 64 | 30 | 04 | 01 | 01 |
| 4 | Pretreatment | 134 | 3.8 | 62 | 33 | 02 | 03 | 00 |
| | Post-treatment | | 5.7 | 56 | 38 | 05 | 01 | 00 |
| 5 | Pretreatment | 138 | 5.9 | 66 | 29 | 03 | 01 | 01 |
| | Post-treatment | | 5.9 | 62 | 30 | 06 | 01 | 01 |
| 6 | Pretreatment | 122 | 5.9 | 60 | 39 | 01 | 00 | 00 |
| | Post-treatment | | 8.6 | 49 | 44 | 07 | 00 | 00 |

of the same parameters, and patients continued to monitor their symptoms as before. Patients went on taking the remedies for a further 2 months, but no further blood samples were drawn.

The symptom scores for each subject were totalled and averaged, compared for before and after treatment, and the results tabulated (*Table 2*). Where appropriate, statistical analysis was performed using Student's *t* test for paired data. Pretreatment and post-treatment NK and LAK cell activities were compared using the Wilcoxon signed rank sums test for nonparametric data.

## RESULTS

*Table 2* shows scores for the individual minor criteria symptoms recorded by subjects before and after treatment. No differences appear in the numeric scores nor in the overall categories before and after treatment. No statistical analysis was performed on the data in *Table 2* because no differences were seen in the raw data between pretreatment and post-treatment.

Hemoglobin, white blood cell count, and differentials before and after treatment are shown in *Table 3*. A general trend toward normalization of the total white count appears over the treatment period. For example, the high initial white count of 15.1 in case 1 is normalized to 10.3; whereas the low white count of 3.8 in case 4 is normalized to 5.7. Even low counts within the normal range tended to increase in four cases. However, these could simply be normal variations over time.

The immunologic markers measured were variable, did not show any consistent abnormalities in the group before treatment, and showed no consistent changes over the course of the study (*Table 4*). Although it appears that CD3+ cells were reduced after treatment in two patients, the differences were not significant for the group as a whole. Markers for NK cells were found to be variable and not significantly different before and after treatment. Activity of NK and LAK cells relative to normal controls was lower than the normal mean in most patients, but was not significantly different before and after treatment (*Table 5*). The mean and standard error of the lytic unit values for the six cases shown in *Table 5* were as follows: NK (pretreatment) = 212 ± 105, NK (post-treatment) = 118 ± 29; LAK (pretreatment) = 84 ± 22, LAK (post-treatment) = 106 ± 38. Much of the variability in the data was attributable to case 5. If case 5 were omitted from the calculations, results among the different donors were more consistent: NK (pretreat-

ment) = 108 ± 19, NK (post-treatment) = 97 ± 24. LAK (pretreatment) = 97 ± 23, LAK (post-treatment) = 82 ± 36. However, analysis of these data still failed to demonstrate significant differences between the pretreatment and post-treatment groups.

## DISCUSSION

The criticism that patients with this type of illness tend to exaggerate their symptoms was not borne out. Only three out of the 16 symptoms were listed as severe; most were scored as moderate, and a few as mild. The symptoms listed as severe were those most consistently reported as major CFS symptoms: debilitating fatigue, muscle aches and weakness, and postexercise fatigue.

In this small uncontrolled case series of six patients, the four agents used in combination did not have any apparent effect, either on a subjective level or on an objective level using immunologic parameters. While this is a disappointing result, several points are worth making. In a syndrome where the symptoms vary over time and where there are remissions and exacerbations of varying degrees, it is important to validate the effect of botanic and homeopathic preparations through appropriate scientific research. A negative result, or confirmation of a null hypothesis, is significant. Although several studies have shown changes in the immune parameters of CFS patients, no consistent and reliable test is diagnostic, or even usually associated with the disease.[8-14]

In this study we observed no differences in pretreatment and post-treatment measurements, and no changes to the normal limits for the markers studied. Although follow-up was not part of the research design, three of the six patients have indicated that their condition did not change significantly over the year following the study. We followed all the subjects for 3 weeks because the naturopathic physician who supplied the remedies indicated before the study that change could be expected within that time. It appears, however, that, in our small case series of CFS patients, the treatment had no effect.

Because diseases such as CFS do not respond well to drugs, and because botanic and homeopathic remedies are becoming more acceptable and popular, it is important that patients have the benefit of confirmatory research regarding the efficacy of the products that they take. When conventional medicine fails patients, they turn to alternative sources for relief. Because remission does occur in CFS patients, often after prolonged periods and quite suddenly, and because CFS patients are often trying many alternative forms of treatment at the same time, it is

*Table 4.* **LYMPHOCYTE MARKERS (CD3, CD16, AND CD56) BEFORE AND AFTER TREATMENT.**

| CASE | TIME | CD3 x $10^9$/L | CD16 x $10^9$/L | CD56 x $10^9$/L |
|---|---|---|---|---|
| 1 | Pretreatment | 1.87 | 0.29 | 0.01 |
| | Post-treatment | 1.14 | 0.25 | 0.30 |
| 2 | Pretreatment | 2.07 | 0.22 | 0.22 |
| | Post-treatment | 1.98 | 0.11 | 0.07 |
| 3 | Pretreatment | 0.86 | 0.12 | 0.12 |
| | Post-treatment | 0.76 | 0.28 | 0.14 |
| 4 | Pretreatment | 0.83 | 0.08 | 0.08 |
| | Post-treatment | 1.16 | 0.12 | 0.24 |
| 5 | Pretreatment | 1.35 | 0.15 | 0.14 |
| | Post-treatment | 0.74 | 0.07 | 0.16 |
| 6 | Pretreatment | 1.43 | 0.48 | 0.44 |
| | Post-treatment | 1.46 | 0.38 | 0.79 |

*CD3 Pan T cell marker, normal range = 0.9 - 2.5 x $10^9$.*
*CD16 NK cell marker (Fc receptor), normal range = 0.2 - 0.5 x $10^9$.*
*CD56 NK cell marker, normal range = 0.1 - 0.3 x $10^9$.*

*Table 5.* **PRETREATMENT AND POST-TREATMENT NK (K562) AND LAK (RAJI) ACTIVITY EXPRESSED AS CYTOTOXICITY RELATIVE TO NORMAL DONOR CONTROLS.**

| CASE | PRETREATMENT NK | POST-TREATMENT NK | PRETREATMENT LAK | POST-TREATMENT LAK |
|---|---|---|---|---|
| 1 | 0.18 | 0.23 | 0.35 | 0.32 |
| 2 | 0.77 | 0.32 | 0.14 | 0.06 |
| 3 | 0.57 | 1.02 | 0.40 | 0.60 |
| 4 | 0.55 | 0.54 | 0.10 | 0.07 |
| 5 | 3.64 | 1.31 | 0.07 | 0.65 |
| 6 | 0.63 | 0.49 | 0.39 | 0.11 |

*Normal relative NK: range 0.37-3.12, n = 30, mean = 1.00, median =1.10. Normal relative LAK: range 0.1-2.3, n = 13, mean = 1.00, median = 1.20.*

important to verify the efficacy of botanic and homeopathic remedies in a controlled way. Only by doing this will we be able to recommend appropriate remedies to our patients. We would encourage further research on these and other remedies that are reported anecdotally to be efficacious. Such research should involve a sufficiently large number of subjects to provide reliable data in a syndrome that is characterized by wide variations in symptoms and laboratory data. Subjects should be placed randomly in placebo and treatment groups, and studies should be further controlled by using a treatment crossover format. However, in spite of anecdotal evidence to the contrary, there is insufficient evidence to justify a trial of this nature to further assess the efficacy of the herbal preparations used in this series of six patients. ■

***Note added in proof:*** *Since submitting this article for publication, we have conducted a study of NK cell numbers and function in 19 CFS patients. In this larger study, NK activity (using a 4-hour $^{51}$Cr-release assay) was found to be significantly lower than controls, total CD56+ cells were increased, and the proportion of CD3-, CD56+ cells was decreased. These data indicate that both the method of measuring NK activity and the measurement of "double" CD3, CD56 marker-bearing cells are important variables in assessing immunologic abnormalities in CFS. Results are in press* (Nightingale Foundation Review.) *Ottawa, Ont: University of Ottawa Press, 1992).*

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