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CORIOLUS
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Chronic Fatigue Immune Dysfunction Syndrome

Chronic fatigue, also referred to as epidemic myalgia, myalgic encephalomyelitis, chronic viral syndrome and post viral fatigue syndrome, is a complex clinical syndrome. It is characterised by incapacitating fatigue, neurological problems and a constellation of symptoms that can resemble many other illnesses.

Definition and Clinical Evaluation of Prolonged Fatigue [2]

Prolonged fatigue is defined as self-reported, persistent fatigue of one month or longer. Chronic fatigue is defined as self-reported persistent or relapsing fatigue of six or more consecutive months.

Symptoms and Signs Of Chronic Fatigue Immune Dysfunction Syndrome

The symptoms include :
- Muscle pain
- Multi-joint pain without joint swelling or redness
- Sore throat
- Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities
- Changes in mood
- Headaches of a new type, pattern or severity
- Un-refreshing sleep
- Tachycardia
- Coldness of the extremities
- Sweating
- Pallor and sluggish pupils
- Post-exertional malaise lasting more than 24 hrs.

The signs include :
- Low-grade fever
- Non-exudative pharyngitis
- Palpable or tender lymph nodes

Causes Of This Syndrome

Amongst the causes are post-viral disruptions of immune functions [PVS]. A variety of viruses have been implicated in the development of CFIDS including Herpes viruses [EBV, CMV, Herpes Simplex and Human Herpes 6 : HHV6], Polio, Coxsackie, Adenoviruses and Retroviruses. Other causes may include chemical exposure [i.e. pesticides and organic solvents exposure].

Tests Performed
- T-lymphocyte subsets

- Natural killer cells : CD3-CD16+CD56+
- EBV Viral Capsid [VCA] IgG and IgM
- EBV Early Antigen [EBEA] diffuse IgG
- EBV Nuclear Antigen Antibody [EBNA],
- EBV Nuclear Antigen IgM
- Human Herpes Virus 6 [HHV6] IgG.
- CMV IgG and IgM

Results

All patients were found to have combinations of high antibody levels to EBV in the groups mentioned and/or HHV6 and/or CMV.

Age range of the patients was between 17 yrs. and 83 yrs. and the female : male ratio was 2 : 1.

T-cells [%CD3+CD26] showed Increased activation in two thirds of the patients before and after review, depression in 22% of patients and 11% remained static.

T-cells [CD3+HLA-DR+] showed activation in 77% and decreased activation in 11%. T-helper suppressor cells were variable in their original presentation.

The normal range of natural killer cells is 5 – 20% and the cell count is 75-1800 cmm. Natural killer cells were found to be low in our patients before treatment, the average being 129.64 cmm.

An increase in natural killer cells following treatment with Coriolus was demonstrated with the average being 175 cmm, which is an increase of 35%.

Discussion

The results clearly show that Coriolus Versicolor has improved natural killer cell numbers in this group of patients.

Coriolus Versicolor

Coriolus Versicolor is a mushroom from the Amastigomycota group of mushrooms. This group of mushrooms is a large and diverse group that does not produce a motile stage and is not adapted to an aquatic environment. It contains all edible and medicinal fungi. There are four subdivisions : Zygomycotina, Ascomycotina, Basidiomycotina and Deuteromycotina.

Coriolus is from the family of Polyporaceae from the Basidiomycetes group. It contains a polysaccharopeptide [PSP] which has been non-specifically used in a number of conditions to alleviate symptoms and prevent a decline in immune status. [3]

It can also enhance superoxide dismutase [SOD] activity [4]. It is thought to protect macrophages from the damage induced by reactive oxygen species by enhancing antioxidant capacity [5]. Activation of peritoneal macrophages by PSP has been shown and an immuno-modulatory effect on the defensive cells was

demonstrated [6].

In view of these findings, Coriolus was used for its effects on host defence potentiation.

Patients were examined and a number of the abnormal findings that are remarked in patients with chronic fatigue syndrome were noted, such as lymphadenopathy and pharyngitis. There was a disturbance of autonomic function in all patients evaluated by Heart Rate Variability.

Heart Rate Variability [Statistics compiled by Dr. Alexey Tarnakin]

Heart Rate Variability before treatment confirmed dysautonomia.

All 36 patients had Heart Rate Variability examination before treatment [31 standing as some were too weak for sustained standing].

The results are presented in Table 1.

Table 1. Heart Rate Variability before Treatment

	HRV before treatment	
	Lying **36 patients**	**Standing** **31 patients**
Mean RR	868±156	774±110
Minimum RR	562	524
Maximum RR	1058	1048
SDNN	45.9	47.7
RMSSD	54.9	39.3
SDSD	54.9	39.3
NN50	46.9	47.8
pNN50	10.5	8.62
Total Power of HRV 3466±1018	2593±954	2706±1420
VLF	374	427
LF 1170±416	247±214	364±686
HF 975±203	220±266	188±255
LF/HF Ratio 1.5-2.0	1.76±1.25	3.11±2.67

Key :
SDNN Standard deviation of the normal-to-normal interval
RMSSD Square root of the mean squared differences of successive NN intervals
SDSD Standard deviation of differences between adjacent NN intervals
NN50 Number of interval differences of successive NN intervals greater than 50 ms.
pNN50 NN50 count divided by the total number of all NN intervals
VLF Very low frequency

The Total Power [TP] of Heart Rate Variability [HRV] was slightly decreased with a mild increase on standing. The Low Frequency component [LF] of TP HRV and the

High Frequency component [HF] of TP HRV were moderately decreased. The LF/HF Ratio was within normal range.

On standing there was a mild increase of LF and a mild decrease of HF with subsequent increase of LF/HF Ratio.

The individual analyses of HRV before Coriolus treatment are presented in Table 2

Table 2

HRV before Coriolus treatment					
Lying 36 patients			**Standing 31 patients**		
RR less 0.67sec	RR 0.67 – 1.0 sec	RR more 1.0 sec	RR less 0.67sec	RR 0.67 – 1.0 sec	RR more 1.0 sec
2	28	6	4	25	2
Total Power of HRV less 2000	Total Power of HRV 2000 - 4000	Total Power of HRV more 4000	Total Power of HRV less 2000	Total Power of HRV 2000 - 4000	Total Power of HRV more 4000
10	22	4	9	20	2
LF less 600	LF 600 - 1600	LF more 1600	LF less 600	LF 600 - 1600	LF more 1600
33	3	0	28	2	1
HF less 700	HF 700 - 1200	HF more 1200	HF less 700	HF 700 - 1200	HF more 1200
33	3	0	30	1	0
LF/HF Ratio less 1.5	LF/HF Ratio 1.5 – 2.0	LF/HF Ratio more 2.00	LF/HF Ratio less 1.5	LF/HF Ratio 1.5 – 2.0	LF/HF Ratio more 2.0
19	4	13	8	6	17

10 out of 36 patients had a decrease in the TP of HRV, 22 out of 36 patients had normal TP of HRV and 4 out of 36 patients had an increase of the TP of HRV.

LF and HF components were decreased in 33 out of 36 patients with LF/HF Ratio less than 1.5 [predominance of vagal tone] in 19 out of 36 patients and with LF/HF Ratio more than 2.00 [sympathetic predominance].

On standing 9 out of 31 patients had a decrease of the TP of HRV, 20 out of 31 patients had normal TP of HRV and 2 out of 31 patients had an increase of the TP of HRV.

LF component was decreased in 28 out of 31 patients with LF/HF Ratio less than 1.5 [predominance of vagal tone] in 8 out of 31 patients and with LF/HF Ratio more

than 2.00 [sympathetic predominance] in 17 out of 36 patients.

HF component was decreased in 30 out of 31 patients.

These results suggest a decrease of the total activity of the autonomic nervous system with altered sympathetic tone.

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macrophages from the damage induced by reactive oxygen species by enhancing antioxidant capacity [5]. Activation of peritoneal macrophages by PSP has been shown and an immuno-modulatory effect on the defensive cells was demonstrated [6].

In view of these findings, Coriolus was used for its effects on host defence potentiation.

The fungus Coriolus Versicolor is found almost worldwide with variations due to habitat. To eliminate these variations, strain CV-OH1 was established some 15 years ago by Gourmet Mushrooms Inc. in California, USA. This CV-OH1 strain demonstrates rapid and aggressive colonisation and far outmatches other isolates in bioactivity and vigour. A mother culture of strain CV-OH1 has been developed and maintained since isolation and this is used to produce the spawn. In-house checks confirm that the mother culture does not move from the original isolate. The production process involves the inoculation of sterile organic edible grain with the spawn from the mother culture. The fungus is allowed to completely colonise the growth medium aseptically and at the correct stage of development, at maximum bio-availability, the living biomass is aseptically air-dried and granulated before testing microbiologically. This technique produces a raw material which is sterile and contains no pesticides, heavy metals, is free from foreign matter and is totally reproducible. The material is shipped to a U.K. GMP Pharmaceutical facility where it is manufactured into 500 mg. tablets with the addition of cellulose, silica, a granulating agent and a tablet press lubricant.

The finished tablet complies with the B.P. requirements for tablets and long-term stability is being established using TVC and PCR. A PCR/electrophoresis method is being established to determine the DNA of this product as an additional method of quality control.

Natural Killer Cells

Natural killer cells are an important first line of defence against newly arising malignant cells and cells infected with viruses, bacteria and protozoa. They form a distinct group of lymphocytes with no immunological memory and are independent of the adaptive immune system. Natural killer cells constitute 5% to 16% of the total lymphocyte population. Their specific function is to kill infected and cancerous cells. McGinnes and Chapman’s method for measuring the function of natural killer cells uses K562 cells as the target cells that are labelled with a fluorescent dye instead of radioactive chromium. Viability is then measured using a flow cytometer. The advantages of this method are increases in specificity, sensitivity and the absence of radioactivity in the assay.

Natural Killer Cells [7]

Viruses lack the apparatus for self-renewal so it is essential for them to penetrate the cells of the infected host in order to take over its replicative machinery. It is clearly in the interest of the host to find a way to kill such infected cells before the virus has had a chance to reproduce. NK cells appear to do just that when studied in vitro.

They are large granular lymphocytes with a characteristic morphology. They are thought to recognise structures on high molecular weight glycoproteins which appear

on the surface of virally infected cells and which allow them to be differentiated from normal cells. This recognition probably occurs through lectin-like [i.e. carbohydrate binding] receptors on the NK cell surface which bring killer and target into close opposition.

Activation of the NK cell ensues and leads to polarisation of granules between nucleus and target within minutes and extra-cellular release of their contents into the space between the two cells, often utilising the cytolysin perforin.

NK cells kill by activating apoptosis.

In addition to perforin, the granules contain tumour necrosis factor β and a family of serine proteases termed granzymes, one of which, granzyme B, can function as an NK cytotoxic factor. Also fully ionised ATP which can cause apoptosis in many different cell types; the effectors themselves are resistant probably due to a lack of ATP receptors on their surface. These factors sequentially induce NK-mediated lysis.

A current view is that granzyme B kills by directly activating an endogenous family of ICE [IL-1β converting enzyme] proteases which subsequently degrade other molecules including the repair enzyme poly [ADP-ribose] polymerase. Chondroitin sulphate A, a protease-resistant highly negatively charged proteo-glycan, is present in the granules and may protect the NK cell from autolysis.

The various interferons augment NK cytotoxicity and since interferons are produced by virally infected cells, there is an integrated feedback defence system.

Virally infected cells can be killed by cytotoxic T-cells and ADCC [8]

Viral antibodies can bring the NK cell very close to the target virally infected cell by forming a bridge and the NK cell being activated by the complexed antibody molecules is able to kill the virally infected cell by its extra-cellular mechanisms. This system, termed antibody-dependent cell-mediated cytotoxicity [ADCC], has been demonstrated in vitro.

Conclusion

We have demonstrated in a group of 36 patients who have had defined chronic fatigue syndrome and autonomic dysfunction that Coriolus MRL has been an immuno-therapeutic agent. It has improved natural killer cell numbers by 35% in this group with a two months course of treatment.

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