

Clinical Data and a Therapeutic Approach to Patients with Chronic Epstein-Barr Virus Syndrome: CEBVS Case Study

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Introduction

Infectious Mononucleosis has been known to physicians since 1920 when it was first described by Sprunt and Evans.¹

However, it seems that the epidemiology of the disease is not fully understood yet.¹² Certain individuals with genetic predisposition or immunologic impairment or strain variation probably hold the factors for the development of chronic active Epstein-Barr Virus (EBV).^{3 4}

Z. B. Katz et al found the same strain of EBV in peripheral blood and in saliva. They concluded that the virus replicates in the oropharynx and supplies an ongoing infection of the lymphocytes. Beside the oropharynx, the second site for EBV is the cervical-uterus from which it is transmitted to the infant.⁵ In their article, Speck and Strominger made the remark that pre-adolescent children infected after puberty, develop a debilitating non-malignant lym-phoproliferative syndrome. EBV is also implicated in the development of some tumors as in Burkitt's lymphoma, naso-faringeal carcinoma, aggressive lympho-proliferative disorders and thymic carcinoma.⁶

The factors contributing to the tumor development are: genetic predisposition, immunologic defects, other infectious agents (other virus or malaria) and environmental co-carcinogens.⁷

In EBV-induced infectious mononucleosis, the initial viral infection of B cells is followed by an extensive proliferation of T cells.^{3 8} The intracellular virus

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stimulates the T-helper cells which help in the maturation of T-cytotoxic cells and release interferons. Interferons released by the infected cells and T-helper cells stimulate Natural Killer (NK) cells and inhibit viral replication directly. Virally infected cells are killed by T-cytotoxic cells and NK cells.^{9 10 11}

In vitro, the infection of B lymphocytes by EBV presents two main characteristics:

1) latency, which means that the virus has a continuous presence in the infected cells without producing viral particles, but presenting patterns of viral transcription

2) proliferation, which represents a growth transformation of the infected B lymphocytes.

Due to an apparent inability of the human body to generate a proper amount of antibody to Epstein Barr Nuclear Antigen (EBNA), the EBV breeds a low grade infection. The virus is considered for this reason to be rather latent than dormant.¹²

Earlier studies done by Jones, Ray and Strauss and his co-workers have tried to explain the role of chronic EBV infections in patients with persistent unexplained illness.^{13 14}

It is established that once an individual has been infected with EBV, the virus maintains a permanent latent infection of B lymphocytes.¹⁵

The nature of the chronic fatigue syndrome as well as its own existence as a distinct disease are still controversial according to Grierson, Holmes and Strauss.¹⁵

There are strong genetic and environmental factors which influence the expression of this disease.¹⁶

Purpose

The purpose of our work was to obtain

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further clinical information on patients presenting chronic fatigue syndrome, suspected of having a chronic EBV infection, including practical data regarding their therapeutic response.

Method

From the patients referred with chronic fatigue or chronic depression syndrome for which no clear cause could be found, we selected for our study a group of 62 adults ranging in age from 20 to 65 years. Based on symptoms as well as on the inability of establishing another immune impaired disorder, all 62 patients were diagnosed as suffering from chronic illness associated with EBV infection, although some had low seropositive titers. Symptoms presented by these patients were mainly fatigue, depression, allergic reactions, headache, mild myalgia and sleep disturbances (Table 1).

All patients had a physical examination and various laboratory tests. Blood specimens were obtained during symptomatic periods.

Laboratory tests included hematology, chemistry, immunology and serology. For viral studies, we tested for anti-IgG-Virus capsid antigen (anti-VCA-IgG) and anti-early antigen (Anti-EA) titre.

Buist¹⁷ mentions that serious consideration and effort must be done in connection with critical symptoms presented by a growing number of patients suffering from prolonged exposure to chemicals.

We examined the exposure to chemicals, antibiotics and emotional stress, as well as reaction to chemicals on our group of patients.

Results (See Tables pages 187, 188)

Hematology tests showed no abnormality for hemoglobin (Hb), hematocrit (Hct) and a slight increase in erythrocyte sedimentation rate (ESR) in 22% of the patients. Only 5% had a few atypical lymphocytes. Chemistry tests showed an increase for alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), vitamin A, total iron binding capacity (TIBC) and a decrease for vitamin B₁₂, tri-iodothyro-nine uptake (T₃), thyroxin radioimmunoassay (T₄), iron and folic acid.

Immunology tests showed no abnormality for immunoglobulin G (IgG) but an increase for

immunoglobulin M (IgM), immunoglobulin A (IgA), C3 complement component (C3) and C4 complement component (C4).

Serology tests showed increased titre for anti-microsomal antibody and anti-thyro-globulin antibody in 25% of the patients and increased C-reactive protein (CRP) titre in 25% of the patients (Table 2).

All 62 patients were tested for VCA and EA. Of these, 44 had elevated VCA titre from which 2% had a titre 1:1280, 35% had a titre 1:640, 34% had a titre 1:320 and 29% had a titre 1:160. 15 patients had a high EA titre from which 2% had a titre 1:160, 2% had a titre 1:80, 21% had a titre higher or equal to (>) 1:40 and 75% had a titre lower than(<) 1:40 (Table 3).

From the total number of 58 patients tested for chemicals, 66% had high exposure, 2% had mild exposure and 32% had no exposure to chemicals.

Regarding exposure to antibiotics, 47% had high exposure, 22% had mild exposure and 31% had no exposure.

As for exposure to emotional stress, 10% had high exposure, eg. death in the family, and 90% had mild exposure, eg. stress at work.

93% had severe, and 7% had mild reactions to chemicals during provocative neutralization testing¹⁹ (Table 4).

Therapeutic Approach for Patients with CEBVS

The prevailing view in the management of CEBVS is that psychological support, physical rest and time are the best cure for that syndrome.¹⁸

Considering the chronic and very debilitating character of this syndrome in some patients, we used a comprehensive management, including rest, psychological counselling as well as ecological treatment.

Management of all our patients included a very careful environmentally-oriented medical history based on the Allergy Data Base and Health History.¹⁹ Each patient underwent environmental and allergy investigation including testing for foods, inhalants, chemicals using sublingual, intradermal or Vega II testing, depending on the patient's severity of clinical reactions.^{19 22}

Table 1
Clinical Features of Chronic EBV Suspected Patients

Symptoms	Patients (n = 62)	Percent %
Fatigue	59	95
Depression	46	74
Allergy	62	100
Headache	43	69
Myalgia	47	76
Sleep Disturbance	38	61

Table 5
Provocative Testing and Therapeutic Response to Fluogen Vaccine

Number of Patients	Provocative Testing		Therapeutic Response	
	#	%	#	%
28	28	100	28	100

Table 6 Therapeutic Response of EBV Patient Treated with Vitamin C, Ca, Mg I.V.

Number of Patients	Positive Response		Negative Response	
	#	%	#	%
18	18	100	0	0

Table 2
Laboratory Tests of Suspected Patients

with Chronic EBV Infection

Laboratory Assay	Abnormalities versus # of patients tested	Percent %
Hematology		
Hemoglobin	0	0
Hematocrit	0	0
ESR*	13/58	22
Atypical lymphocytosis	3.41	5
Chemistry		
Al. phosphatase 1	3/44	7
SGOTI	3/42	7
Vitamin A	8/59	22
Vitamin B ₁₂ i	2/58	3
Folic Acid ♦	12/58	21
T ₃ Uptake ¹] i T ₄	9/59	15
Total J ⁱ	8/59	14
Iron ♦	15/52	29
TIBCf	9/52	17
Immunology		
Immunoglobulin G	0/60	0
Immunoglobulin Mi	18/60	30
Immunoglobulin Af	2/60	3
Complement 31 *	6/57	11
Complement 4J	9/57	16
Serology		
Microsomal antibody 1	11/59	17
Thyroglobulin antibody f	5/59	8
C.R.P.f	14/55	25

t : increased
J : decreased

Table 3 Serologic Tests for Chronic EBV Suspected Patients

Patients	Viral Capsid Antigen (VCA) Titer	VCA %	Patients	ft	█ █ █	%	EA
1	1:1280		2	1		1:80	2
22	1:640		35	7		> 1:40	11
21	1:320		34	6		1:40	10
1	1:160		2	1		1:160	2
17	1:160		27	47		<1:40	75
62		100	62				100

Table 4 Exposure and Reaction of Suspected CEBV Patients

Total # of patients and age range	Exposure to Chemicals		Exposure to Antibiotics		Exposure to Emotional Stress		Reaction to Chemicals during Provocative Testing		
	Pat. #	%	Pat. #	%	Pat. #	%	Pat. #	%	%
58 14-60 years	High:	38 66	High:	27 47	High:	6 10	Severe:	54	93
	Mild:	1 2	Mild:	13 22	Mild:	52 90	Mild:	4	7
	Not exposed:	19 32	Not exposed:	18 31	Not exposed:	0 0	No reaction:	0	0

All patients were put on a 4-day rotation and elimination diet as well as environmental modification according to Clinical Ecology management.²⁰ This included elimination of the foods to which the patient was allergic or intolerant and rotation of safe foods on a 4-day basis.

Neutralization desensitization for inhalants and chemicals was carried out for the majority of patients either by sublingual or intradermal method.^{21 22} Therapy for mucocutaneous candidiasis was used for many patients.²³

From all 62 patients, 28 with flu-like symptoms were subjected to provocative neutralization testing with fluogen vaccine.²⁴ All 28 of the patients during provocative neutralization testing showed flulike symptoms and were neutralized. The neutralization dose of 0.05 cc of Fluogen was given once per week or more often depending on the symptoms. This group of patients presented an improvement of between 70-100% (Table 5).

Another 18 patients were treated with an antiviral and immune stimulating substance such as vitamin C, 7-14 gm given intravenously (I.V.) over 1-1 1/2 hours.^{25 26 27 28 29} Response to this therapy was 100% (Table 6). The improvement and almost complete elimination of symptoms lasted only 5-7 days, after which the therapy had to be repeated. Usually, a patient got one I.V. per week for 5-6 weeks.

Each patient on I.V. infusions was also receiving 20 mEq of magnesium sulphate to treat hypomagnesemia, low red blood count (RBC) of magnesium and an increase in urinary excretion of magnesium.³⁰ This treatment was very helpful in improving muscular spasms, joint and bone pain.

11 patients with low serum iron received a therapeutic dose of iron (6 mg/kg/24 hours) in divided doses for 6 weeks followed by 1 tablet of iron once a week for one month.

There were 15 patients with thyroiditis and some disturbance with their thyroid function related to recurrences of viral symptoms. At that time, they had some discomfort in the neck area and swelling of the thyroid gland as well as difficulty in swallowing.

These patients usually had either elevated anti-thyroid microsomal antibody or anti-thyroglobulin antibody. Patients with typical

hypothyroidism, low T₄ or T₃ and elevated thyroid stimulation hormone (TSH) received regular thyroid replacement therapy with Elthroxin.

Patients with normal T₃, T₄ and TSH but abnormal anti-thyroid antibodies, also showing abnormal function of thyroid by Bioenergetic Regulatory Technique (BER) (using the Vega II method³¹) were given thyroxin RN sublingual drops, according to rapid neutralization technique.³²

All patients with abnormal antibody titre to thyroid additionally received 5% potassium iodide (5% KJ) 1-2 drops/week. This approach helped the patients to maintain a high energy level.

Since some patients infected with the EB virus show an inability to fight the infection, it seems reasonable to use stimulants for the immune system either through direct stimulation of interferon by staphylococcus lysate^{33 34**} or through stimulation of Interleuken 2 (IL-2) by thymus extract.^{35 36}

Staphylococcus lysate was used by Miller's method²² with increments of 0.05 cc of neutralizing dose every day by subcutaneous (S.Q.) injections until redness of the skin appeared to a size of 2.5 cm. Then the latest dose was used once per week S.Q.

Use of the Transfer Factor should also be considered in patients with CEBV.³⁷

Discussion

In 1970, Verloop in his article "Iron depletion without anemia: A controversial subject" established that some patients have low serum iron (latent iron deficiency) and depleted storage iron without anemia.³⁸

Morrow had established even two years earlier that fatigue occurs in latent iron deficiency, although anemia was not present.³⁹

Beutler et al determined that about two-thirds of a group of chronically fatigued non-anemic women, subjected to iron therapy showed an improvement of their symptoms.⁴⁰

Dr. F. Pitts, presenting at the Fourth Annual Medical Symposium on the Effect of the Environment on Man, in Toronto in 1988, stated that half of the 300 CEBV patients studied had serum iron level

below the reference range. Following treatment with the deficient cation, almost all patients showed improvement with relief of specific symptoms.³⁰ Their clinical observations and virological studies would agree with our observations.

From 23 patients described by Strauss and colleagues, most had high VCA and EA titre.¹⁵

Both Strauss and Jones support the existence of an active infection. Some of their patients had periods of exacerbation occurring from 1 to 6 times a year with prolonged periods of disability.^{15 16} We observed the same pattern in our patients.

Mukherjee has established that during a relapse, red cells lose their ability to enter the capillaries and therefore negatively affect the normal function of the cells.¹⁷

Robert Buist, discussing chronic fatigue syndrome, assumes that symptoms presented by patients suffering from this disease, could be owed to a deficiency of the red blood cells.¹⁷

Buist also mentions that serious consideration and effort must be taken in connection with critical symptoms presented by a growing number of patients suffering from prolonged exposure to chemicals.

Organochlorines are especially dangerous to humans due to their ability to block nerve conduction. They induce reversible red cell deformation which, as a consequence, weakens the immune system.

In our study, exposure to chemicals included: exposure to general volatile substances (GVs) such as benzene, styrene, trichloroethylene either at home or at work; pesticides and herbicides during repetitive use at home, garden or school; paints and glues used at home or school, as well as construction materials used during renovations of offices, schools and homes.

Overuse of antibiotics for recurrent infections and medications for depression and allergies were other causes of excessive chemical load in our patients with CEBVS.

Conclusion

Although we realize that it is not a cure, the therapy applied to the CEBVS patients as described above can provide them with a substantially improved physical state as well as with a better way of life. However,

it would be simplistic to see only the EBV infection in so many patients suffering today from chronic fatigue syndrome.

The causes are multiple and one has to look at the patient and his surrounding environment. This environment is becoming more polluted daily. Water, food, air, homes and workplaces are contaminated. We must remember that we are dealing with a globally compromised immune system in the whole human species. Infections with bacteria, fungus, viruses and parasites are only an expression of our diminished defense against them. To better fight these infections, we must learn to live in harmony with our environment.⁴¹

Case Study

D.B., a 27 year old female was first seen in March 1987. Among her chief complaints were asthma which she suffered from since age 3. Generally better in the wintertime and usually controlled with antiasthmatic medications and allergy shots, the asthma had worsened not long before her visit. Gastrointestinal (GI) problems which had plagued her since age 6 had also been aggravated recently. She suffered abdominal pain and bloating as well as constipation alternating with diarrhea.

There was some improvement at age 10 after elimination of apples, cheese and peanuts from her diet. She continued to have cravings for sugar, chocolate, orange juice and peanut butter. Central nervous system (CNS) and psychological problems included restlessness and impulsiveness, changes in mood, tearfulness and depression for no reason, excessive tiredness and insomnia, beginning 1982. Her depression was cyclical in nature, occurring every three months. All GI and CNS symptoms were aggravated five days prior to onset of menstruation. The premenstrual syndrome (PMS) developed over 1981-82.

Her past history included chronic recurrent seasonal ear infections with numerous use of antibiotics since age 3. She had arthritis in hands and feet with generalized muscular pain. In 1982, at the age of 22, she suffered her first bout with mononucleosis and in 1986, at age 26, her second bout. After 1981 all her symptoms became aggravated and uncontrollable. During

that year she lived in a small, poorly ventilated room with excessive exposure to formaldehyde from fabrics used in sewing. The university quarters were sprayed with pesticides. In 1983 she took on a summer job reconstructing an Indian log house. From 1984-88 she took a permanent job with the Conservation Authority working in the same log house. It had been constructed of raw cedar wood with fire retardants and had a dirt floor. Fungicides were used to control excessive mold and wood burned in the fireplace was preserved with creosol. Prior to 1981, from age 6 to 19, she had lived three miles from a BP and Shell refinery.

Laboratory investigations included decreased T₃ of 0.32 (N 0.35-0.45), increased microsomal antibody of 100 (N 100), increased thyroglobulin antibody of 100 (N 100), negative TSH, increased IgE of 1408 ug/L (N 240), increased IgM of 352 (N 45-250). An EBV study showed VCA at 1:640. Her EA was 1:40. A sputum sample showed moderate growth of *Candida albicans*. Ecological investigations included inhalant sensitivity for all indoor and outdoor inhalants (housedust, grasses, weeds, ragweed as well as grass, tree and weed terpens) and chemical sensitivity to synthetic ethyl alcohol, formaldehyde, tobacco smoke and perfume. She was tested for 49 foods, found severely sensitive to 6 and mildly to moderately sensitive to 29. Her Fluogen vaccine neutralizing dose was #3. She was diagnosed as suffering from environmental hypersensitivity disorder, mucocutaneous candidiasis and CEBV infection.

Management included environmental control at home. She was placed on a 4-day rotation and elimination diet with specific emphasis on a yeast-free diet. It was recommended she use safe and tolerable water. Therapy for mucocutaneous candidiasis was begun and desensitization for inhalants and chemicals was instituted. She received supplemental, tolerable vitamins, minerals and free fatty acids in the form of linseed oil. She was also given I.V. infusions with Vitamin C, Ca and Mg as well as weekly injections with the ND #3 for the Fluogen vaccine.

Follow-up visits indicated an overall major improvement. There was a considerable decrease in the number of infections as well as decreased

sensitivity to allergens. The diet stabilized her CNS symptoms (less hyper) and cleared up her GI symptoms. Fluogen injections controlled recurrent flu-like symptoms. A new awareness of the causative factors in her illness increased successful self-management.

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