Report
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EPSTEIN-BARR VIRUS REACTIVATION AND AUTOIMMUNITY IN CHRONIC PAIN CONDITIONS

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INTRODUCTION

The ubiquitous virus, Epstein-Barr has now been determined to be a contributing factor to several chronic painful conditions.[1-5] Although precise causation mechanisms have not yet been fully clarified, EBV may initiate and/or propagate chronic pain conditions by either reactivation and/or by initiating an autoimmune process.[5,6] To date, the general view that EBV is just a nuisance disease that causes mononucleosis, the 'kissing disease," appears to have minimized concern regarding EBV's serious complications. EBV now accounts for 2 to 5% of the world's cancers and is a causative factor in the development of several painful conditions including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and adhesive arachnoiditis.[2,6-8] In summary, the impact of EBV and painful conditions is not yet taken with the seriousness it warrants. Some studies have shown that EBV can create neuroinflammation in glia cells of the central nervous system (CNS) that lead to central pain, also called central sensitization.[9-13] EBV can cause painful medical conditions by interactions with genetic codes, reactivation and colonization, and by creating a chronic autoimmune process.[14-17] These three mechanisms are reviewed here along with testing and treatment recommendations.

EBV treatment is ancillary and not a substitute for standard pain therapy. That said, pain patients with EBV often report pain reduction following EBV treatment measures. EBV testing and treatment should now be incorporated into pain management for serious chronic pain conditions.

PAINFUL MEDICAL CONDIITONS ASSOCIATED WITH EBV

Some specific chronic pain conditions have been found to be associated with abnormal EBV antibodies including those that indicate past or present reactivation and autoimmunity. The first painful disease in this category was sarcoidosis. It has been followed by elevated antibody test levels in Hodgkin's, rheumatoid arthritis, systemic lupus, multiple sclerosis, fibromyalgia, and adhesive arachnoiditis among others. (Table One)

Today, most chronic pain conditions are broadly labeled and categorized as neuropathic, arthritic, headache, or spinal pain. In clinical pain practice, chronic pain patients may have multiple painful conditions. These patients can arguably be labeled as "multi-system chronic pain disease." The authors have obtained EBV antibody tests on many chronic pain patients who have multiple chronic pain conditions. The percentage of patients who have elevated EBV antibody levels is high and provides a plausible reason for the presence of multiple pain conditions. Our experience suggests that all severe chronic pain patients should now be tested for EBV reactivation and autoimmunity.

CLINICAL TESTS AND INTERPRETATION

Five blood tests are now readily available for EBV testing of chronic pain patients. (Table Two)

1. IgM Antibody: This test is based on early formation of an antibody usually abbreviated EBV IgM. It is essentially a test for acute infectious mononucleosis. Interpretation: a small percentage (i.e., about 5%) of chronic pain patients may harbor chronic infectious mononucleosis.
2. IgG Antibody: This antibody, usually abbreviated EBV VCA IgG, is formed by the EBV capsule. It rises with each reactivation, and its total serum value represents the summation of past reactivations. Interpretation: high blood levels indicate recurrent, past reactivations that could initiate colonization and autoimmunity.
3. EBV NA IgG: This antibody is formed by the viral nucleus. It is now considered a marker of autoimmunity. Interpretation: high serum levels should be regarded as a marker of past autoimmune assaults on tissue and a high possibly that current autoimmunity is present and active.
4. Early EBV NA IgG: This is the first nuclear antibody that is formed. Interpretation: elevation above normal is a marker that reactivation has occurred.
5. Polymer Chain Reaction DNA: This test is considered the gold standard for reactivation of EBV. A positive test calls for an aggressive attempt to eliminate the virus.

EBV REACTIVATION AND COLONIZATION

EBV is a ubiquitous herpes virus that normally enters the human body during infancy. It may produce signs and symptoms of an upper respiratory infection, at that time, but the virus then enters beta lymphocytes to begin a lifetime of dormant, parasitic existence. EBV's parasitic symbiotic existence is normally symptomless and harmless. The exception may occur when someone experiences a stressful event or occurrence that renders their usual immune defenses incapable of holding the virus in parasitic status.[18-22] EBV is clearly opportunistic and will reactivate if normal immune defenses are impaired.[23] Once reactivated an EBV chronic disorder is established. Multiple studies show that any stressful event that may suppress the biologic stress system including the hypothalamus-pituitary-adrenal-axis may allow EBV to reactivate.[20,22,25]

Once reactivated, the virus enters the blood stream and can be detected by polymer chain reaction testing that assesses the presence of viral DNA. Reactivated virus may cause infectious mononucleosis or other acute diseases. More commonly, however, the virus will invade and colonize in a variety of tissues that may lead to chronic pain. There seems to be a predilection for colonization of lymph nodes, soft tissues such as cartilage and intervertebral discs, and neuronal tissues including glial cells, small nerve fibers, arachnoid membrane, and cauda equina. Clinical observation by the authors suggests that reactivated EBV has a special attraction to

injured or inflamed tissues and the collagen-deficient tissues of Ehlers-Danlos Syndrome, the most common genetic connective tissue disease.

EBV was initially discovered by virologists, Epstein and Barr, who discovered the live virus in Burkitt's lymphoma which is primarily a children's cancer found in Africa.[24] Outside of cancer colonization, there are no studies yet done that verify colonization in such diseases as fibromyalgia, arachnoiditis, or multiple sclerosis. Colonization is presently a presumed clinical diagnosis.

TABLE ONE

SOME MEDICAL CONDITIONS ASSOCIATED WITH EPSTEIN-BARR VIRUS

Diabetes Type A	Adhesive arachnoiditis
Celiac disease	Sjogren's syndrome
Sarcoidosis	Hashimoto's thyroiditis
Rheumatoid arthritis	Multiple sclerosis
Systemic lupus	Carcinoma (nasopharyngeal, gastric,
Fibromyalgia	Hodgkin's, Burkitt's lymphoma)
Myalgic encephalomyelitis/chronic fatigue syndrome (MECFS)	

EBV CREATES AUTOIMMUNE ISORDERS

Autoimmunity is a pathologic process in which some body elements mistakenly attack and destroy normal tissue under the false belief that the tissue is diseased. Simply put, autoimmunity is when your own immune system starts attacking healthy cells within your body. The most deleterious manifestation of EBV, but yet poorly understood, is EBV's proclivity to create autoimmunity when it reactivates.[2,5,6] It is quite clear that the autoimmune process of EBV may exist for years and cause continuous inflammation, tissue destruction, and pain in biologic tissues. Autoimmune assault is mediated either by EBV autoantibodies or by another autoimmune process now called cellular mimicry.[4,5] This is a newly discovered concept. The virus enters a normal cell and changes it into an autoimmune cell which then may begin attacking neighboring, normal cells. Cellular mimicry is now being suggested as a causative factor in chronic inflammation and pain that doesn't resolve. For example, it is well known that inflammation in such autoimmune conditions as rheumatoid arthritis and systemic lupus can be suppressed but not eliminated.

Another serious aspect of EBV autoimmunity is its effect on the CNS. Autoimmune assault is now considered to be a likely cause of glial cell neuroinflammation with the consequence of central sensitization also called central pain. To date, the authors believe we now see cases of significant central pain reduction with suppression of EBV autoimmunity.

WHO SHOULD BE TESTED AND TREATED?

We recommend that severe chronic pain patients be tested and treated for EBV. A simple definition for severity, for example, is the patient who must use daily opioids or neuropathic drugs for relief. Another, simple, clinical determination of severity is the patient with multiple pain conditions.

Prevention and treatment measures for EBV are recommended if both the IgG VCA ad EBNA antibody tests are twice the normal limit. If both antibodies are at least two times normal, it can be assumed that the patient has had recurrent reactivations and has some degree of autoimmunity which likely propagates the patient's painful condition. A patient who shows current reactivation by the early EBNA IgG antibody or PCP DNA tests will need attempts to suppress the virus. It is important to point out that the antibodies, VCA IgG, and EBNA may elevate to very high levels, and they do not go down with treatment.

TREATMENT OF EBV

We recommend some treatment measures be initiated if a patient has a severe, chronic pain condition and elevations of VCA and EBNA antibodies greater than two times their normal limit. Treatment measures are in these three categories (See Table):

1. Prevention of reactivation
2. Suppression of reactivation
3. Tissue protection

A number of medicinals in research settings have been shown to inhibit EBV reactivation[22] (See Table). The one most studied is apigenin (natural flavonoid) and we recommend it with vitamins C, selenium or zinc, and a coconut derivative called monolaurin.[26]

If a patient shows EBV reactivation suppression will have to be attempted. We recommend an ivermectin trial of 9 to 18 mg for 10 days. If symptoms improve, it can be used for maintenance at a dose of 6 to 9 mg on 1 to 3 days a week.

Antiviral therapy should be considered.[27] (Table Four) Although not effective in every case, EBV reactivation is a serious matter, and the possible benefits of antiviral therapy outweigh the risks. For example, in a study of fibromyalgia patients, a combination of famciclovir and celecoxib brought about considerable relief.[28] Although antiviral therapy may not eliminate or totally suppress reactivation, it may still have some suppression effects. The most common antivirals are valacyclovir (Valtrex) and acyclovir.

The third measure is to protect tissues from continuous degradation from either viral colonization of tissues or incessant autoimmune assault. It has long been known that corticosteroids suppress EBV. We recommend low dose, intermittent maintenance with either prednisone or methylprednisolone. Prednisone 5 mg, given 1 to 3 times a week, is for non-spinal conditions and methylprednisolone 4 mg for spinal conditions on 1 to 3 days a week is recommended. Besides a corticosteroid, an anti-inflammatory agent is recommended.

EBV SUMMARY TABLE FIVE
TREATMENT OF EPSTEIN-BARR VIRUS

Criteria for Treatment

- Presence of a chronic painful condition
- Elevations of viral capsid antibody (IgG VCA) and Epstein-Barr nuclear antigen antibody (IgG EBNA) two or more times upper limit of normal

Prevention of Reactivation

- Vitamin C, 1000 – 2000 mg a day
- Zinc or selenium daily
- Apigenin, 50 – 100 mg a day
- Monolaurin daily, 1000 mg a day

Suppression of Reactivation

- Ivermectin 9 to 18 mg a day for 10 days followed by 3 to 6 mg one to three times a week
- Options: An antiviral agent

Tissue Protection

- Methylprednisolone (4mg) or prednisone (5mg) 1 to 3 times a week or pregnenolone and DHEA 100 to 200 mg twice a day
- Ketorolac 10-30 mg 1 to 3 times a week or diclofenac 50 – 100 mg a day

TABLE TWO The Three EBV IgG Antibody Tests Essential For Determination of Reactivation and Autoimmunity			
	Name of Test	Initials and Antibody	Interpretation of Elevation
1	Epstein-Barr Viral Capsid Antigen Antibody	VCA IgG	There have been one or more past reactivations.
2	Epstein-Barr Nuclear Antigen Antibody	EBNA IgG	Autoimmunity has damaged tissue, produced inflammation and chronic pain.
3	Epstein-Barr Early Antigen Nuclear Antibody	EA EBNA IgG	EBV is currently reactivated and causing active autoimmunity.

TABLE THREE

MEDICINALS FOR INHIBITION
OF EPSTEIN-BARR VIRUS REACTIVATION

Vitamin C
Vitamin D
Resveratrol
Luteolin
Astragalus
Curcumin
Andrographis
Cimetidine
Selenium
Zinc
Lysine
Apigenin

The medicinals listed here have shown under laboratory research conditions that they prohibit EBV reactivation.[22,26]

SUMMARY

It is clear that EBV is a causative factor in many chronic pain conditions including some cancers. This virus is ubiquitous and is generally perceived as a nuisance virus that causes infectious mononucleosis, known as the "kissing disease." Consequently, EBV has not been considered a serious health issue, but the scientific and clinical evidence compels that EBV testing and treatment now be a component of chronic pain management.

The pathologic characteristics whereby EBV causes a painful condition is complex and may take place over several years and possibly a lifetime. The seminal event whereby EBV begins its pathologic process is reactivation. Essentially, all humans carry EBV as a symptomless parasite. Under stress, physical or psychologic, one's immune system may allow EBV to reactivate. During reactivation, two pathologic events may occur that can initiate a painful condition in a multitude of body tissues. The virus can invade, colonize, and destroy tissue or produce tumors including cancer. EBV was originally found in Burkitt's lymphoma where it colonized. The second pathologic process that may occur during reactivation is the development of an autoimmune disorder that attacks tissue, causing inflammation, destruction, and pain. EBV autoimmune disorders are due either to the production of autoantibodies and/or a cellular transformation called cellular mimicry. Enough scientific information has now accumulated to recognize that EBV autoimmunity may be responsible for chronic inflammation seen in chronic pain conditions. We recommend specific treatment measures in a chronic pain patient who has the two primary EBV antibodies two or more times normal. Treatment consists of three components: (1) prevention of reactivation, (2) suppression of active virus, and (3) tissue protection from autoimmunity. Although it is a new and unexpected discovery, EBV reactivation and autoimmunity is a causative factor in many chronic pain conditions. Testing and treatment of EBV should now be a component of pain management.

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