“I learned so much reading this incredible work!” – Dr. Joseph Pizzorno ND
“This book should be in the hands of every healthcare professional in the world and every patient who struggles with chronic infections of any kind.”
– Dr. Jessica Drummond, DCN, CNS, PT

Dr. KASIA KINES
Doctor of Clinical Nutrition

THE EPSTEIN-BARR VIRUS SOLUTION

The Hidden Undiagnosed Epidemic of a Virus Destroying Millions of Lives through Chronic Fatigue, Autoimmune Disorders, and Cancer
Once infected, always infected... As discussed before, the virus remains dormant throughout your life until opportunity allows it to activate. It is pleomorphic (of different forms), so it can switch from latent (dormant) to lytic (active) at any time (which we now know is not so much spontaneous as it is driven by external factors), infecting your B cells (and/or T cells) and hiding inside them, thus eluding the immune system and being allowed to replicate inside those B cells until the time comes to lyse again and re-infect you.

Because of its chronic nature, EBV can contribute to various conditions and, not surprisingly, can easily be missed: it has been well studied as a causal or contributing factor of many (including autoimmune) conditions. In fact, “viral infection, including Epstein-Barr virus (EBV), is one of the most frequently considered environmental factors involved in autoimmunity” [1].

Here are examples of autoimmune conditions linked to EBV. This is not an all-inclusive list; it’s just a few samples of studies to give you
the sense of the gravity of EBV. I found that the more I looked, the more conditions I discovered, so at certain point, I had to stop looking.

A Laundry List of CAEBV and Autoimmune Conditions

- **Chronic Fatigue Syndrome (CFS):** It is established that many cases of CFS follow an acute viral infection [2]. Studies of patients with infectious mono caused by EBV show that a small proportion will not recover from post-infection fatigue and later develop CFS [3].

- **Multiple Sclerosis:** “Epstein-Barr infection as indicated by positive serology is an **obligatory precondition** for multiple sclerosis, which is a stronger attribute than a risk factor only” [4]. Moreover, epidemiological studies suggest that childhood EBV exposure is an important determinant of MS risk [5]. In a group of 108 patients with MS, 100% had antibodies to EBV as opposed to other viruses. Nineteen of these patients were followed monthly for one year, and positive early antigen and serum DNA (which indicate current reactivation) were found in 72% of those with exacerbations during that year and none in the group with the clinically stable disease, suggesting that EBV may be the activator of the underlying disease process [6].

- “Neuroinflammation, including the entry of autoreactive T cells, likely follows a breach of the blood-brain barrier (BBB) leading to CNS [central nervous system] lesions in MS.” BBB is a safety barrier of circulating blood and the brain’s extracellular fluid that is supposed to prevent any dangerous constituents from entering the brain; it contains both astrocytes and endothelial cells. Astrocytes are immune cells of the brain—we will discuss them in detail later, as they are very unique in their capacity to turn off. EBV can infect human BBB cells leading to increased production of pro-inflammatory mediators that result in immune cell adherence, thus modeling a key step in MS pathogenesis [7].
While functional medicine is focused on leaky gut, an additional concern for a person with CAEBV or MS should also be a leaky brain. I also agree with Dr. Aristo Vojdani that the gut is not always necessary for pathogens like EBV to have direct access into the brain.

- **Parkinson’s Disease**: Molecular mimicry—there is a hypothesis that in genetically-susceptible individuals, anti-EBV latent membrane protein antibodies targeting the critical repeat region cross-react with the homologous epitope on alpha-synuclein and induce its oligomerization [8].

- **Hashimoto’s Thyroiditis (HT) and other Autoimmune Thyroid Disorders (AITD)**: Research has ample support for EBV’s involvement in thyroid-related autoimmunity. For example, initiation of Autoimmune Thyroiditis may start with latent EBV infection of follicular epithelium [9]. People with HT are reported with latent membrane protein 1 (LMP1) and elevated Epstein-Barr nuclear antigen (EBNA). IgG-VCA and IgG-EA-D/DR are more common in patients with thyroiditis [10]. Graves’ disease coexists with IM due to primary EBV infection, and increased thyrotropin receptor antibodies (TRAb), which is one of the markers of Graves’ disease, are seen in children with IM due to primary EBV infection. Thyroid dysfunction is epidemic [11], and HT is the most prevalent autoimmune thyroid disorder and the most common cause of hypothyroidism in the U.S. [12]. Thus, this population should be tested for EBV.

- **Sjogren’s Syndrome (SS)**: Salivary gland biopsies in SS contain increased levels of EBV DNA compared to normal salivary glands, indicating viral reactivation and inability of lymphoid infiltrates to control EBV replication in people with SS [13].

- **Autoimmune Hepatitis**: As I mentioned before, acute hepatitis can be caused by IM (infectious mononucleosis) [10]. It is usually self-limiting, with mildly elevated transaminases, and less

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5 *Alpha-synuclein* is a major constituent of Lewy bodies, protein clumps that are the pathological hallmark of Parkinson’s disease.

6 *Follicular* cells are cells in the thyroid gland that are responsible for the production and secretion of thyroid hormones thyroxine (T4) and triiodothyronine (T3). Epithelium is the outer layer of the cells.
frequently with jaundice [14].

- **Systemic Lupus Erythematosus (SLE):** SLE may be caused by molecular mimicry: EBNA-1 antibody cross-reacting with lupus-associated autoantigens [10] [15]. There is ample evidence that Lupus is indeed triggered by CAEBV.

- **Rheumatoid Arthritis (RA):** Studies show cross-reactivity between EBV and human self-proteins, presence of the EBV genome in synovial membrane, and a cell-mediated response to the EBV within the joint [16]. In addition, EBV encoded proteins share antigenic and sequence similarity to proteins found in the synovial (joint) tissues. Finally, lymphocytes from patients with RA have decreased ability to limit outgrowth of their EBV infected lymphocytes [17]. We will return to RA soon in a discussion of citrullination.

- **Atherosclerosis:** After reactivation, EBV encodes an enzyme dUTPase, which then tells monocytes in your peripheral blood to make inflammatory cytokines like interleukin-6 and to express an intercellular adhesion molecule-1 (ICAM-1). All this can cause acute coronary events like a heart attack [18]. Interestingly, dioxins have been shown to not only reactivate EBV [19] but also to cause atherosclerosis, even at a low-dose exposure level [20]. We may have to rethink heart health.

- **Juvenile Idiopathic Arthritis:** It is possible that it is driven by infections, including EBV [21]. A new study from 2018 suggests a mechanism in which EBNA2 protein from the virus recruits human proteins to bind to genome of the infected cell—this can cause activation of human genes associated with risk of JIA [22].

- **Celiac:** The same study from 2018 that discusses EBV’s ability of EBNA2 and its related transcription factors to affect regulatory genes associated with autoimmune disorders also adds celiac to the list (along with JIA, MS, RA, IBD, and type 1 diabetes) [22].

- **Mixed Connective Tissue Disease:** There is a possibility of pathogenic role of EBV in this condition [23] [24], although more studies are needed.
• **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):** Patients with CIDP show impaired B cell expression of the inhibitory Fc-y receptor, which alters the state of EBV persistence, causing increase in viral replication and antiviral immune response [25].

• **Type 1 Diabetes** [26]: Human enteroviruses in general are associated with type 1 diabetes, for example, by damaging beta cell of the pancreas and molecular mimicry [27]. EBV is one of many viruses that are associated with this condition [28]. And, we just discussed the 2018 study on EBNA2 causing the expression of genes associated with autoimmunity, including type 1 diabetes [22].

• **Scleroderma** (systemic sclerosis): This has been associated with bacterial and viral infections, including EBV [29]. It has been suggested that EBV modifies the monocyte inflammation in scleroderma: by replicating during infection, EBV strongly

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**Figure 12. Possible mechanisms for virus-induced diabetes.**

Source: Hee-Sook Jun (2004)
induces expression of the toll-like receptor TLR8 in infected primary monocytes in scleroderma [30].

- **Glomerulonephritis** (autoimmune infection in the kidneys): This can be induced by EBV [31], while post-infectious glomerulonephritis can be caused by coinfection of EBV and group A beta hemolytic streptococcus [32].

One thing is critical: if you have any of these conditions, you have failed to improve with previous treatments, and you have NOT tested for EBV, do your diligence and test for it right away.

Let’s now look at Chronic Fatigue Syndrome—it deserves a much closer look because severe chronic fatigue is the number one complaint plaguing people with EBV. We will also visit some other medical complications related to EBV that may be part of your struggle.

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<th>CATEGORY</th>
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<td>Other designations or acronyms in the literature</td>
<td>Chronic symptomatic EBV infection, chronic mononucleosis, chronic active EBV infection (CAEBV), chronic fatigue and immune dysfunction syndrome (CFIDS)</td>
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**Figure 13. EBV chronic infection and associated clinical syndromes.**

Source: Eligio (2010)
Chronic Fatigue Syndrome (CFS) – An Autoimmune Poster-Child of CAEBV

Immunologic abnormalities in CFS are consistent with EBV-induced “chronic viral reactivation syndrome.” In a group of 30 individuals with CFS, all had multiple immunological abnormalities: low natural killer cell cytotoxicity but elevation in numbers, decreased gamma interferon, significantly altered peripheral blood lymphocytes, and elevated numbers of B cells, to name a few [33]. But did you know that CFS used to be called “chronic Epstein-Barr syndrome” [34]? I already stated that a small percentage of patients with IM fails to recover from post-infection and subsequently goes on to develop CFS [3], which could also be what we referred to before as the chronic mononucleosis syndrome. The substantial overlap between CAEBV and CFS has been proposed by Eligio (2010) in Figure 13.

In one family medical practice, 21% of 500 unselected patients seeking primary care for any reason were found to be suffering from chronic fatigue syndrome consistent with CAEBV infection [34]. Symptoms included severe fatigue, usually cyclic, for a median of 16 months (ranging from six to 458 months, and no, it does not seem to be a typo: that is up to 38 years!), associated with sore throat, myalgias (muscle pain), or headaches; 45% of the patients were periodically bedridden, but they did not have a recognizable illness. While this study cautions against claiming that any of these cases were caused by EBV, this is where proper testing and test interpretation of EBV would be instrumental. Any medical practice could run a similar study internally and test all the EBV suspected patients. Will any medical doctor take me up on this challenge?

Citrullination of Arginine and Autoimmunity

There are a number of possible reasons why EBV wreaks havoc on the human body and has been linked to so many autoimmune disorders in the way other viruses have not, which confuses even the best clinicians. I just pointed to the new 2018 study looking at EBNA2 and its related
transcription factors and how they can turn on regulatory genes associated with autoimmune disorders. What it means to you is that out of the blue you develop ulcerative colitis, rheumatoid arthritis, celiac, or more. We also know that an existing immune impairment or suppression is a likely invitation to EBV damage.

There is yet another mechanism of EBV-related autoimmune disorders: citrullination. According to my interview with Dr. Aristo Vojdani, PhD, the world expert on immunology who runs hundreds of EBV tests, EBV is the only virus that causes citrullination of proteins [35], so let’s add that property to the list of problems associated with CAEBV.

Citrullination (or deamination) is the conversion of the amino acid arginine in a protein into the amino acid citrulline. This deamination of arginine side chains in protein results in the loss of a positive charge and an increase in local hydrophobicity for the target protein. There is a whole list of implications such as protein unfolding or loss of protein, and citrullination seems to be a physiologically important process as well, but of our interest is unveiling of novel antigenic epitopes that can elicit immune responses and autoimmunity. Citrullination has been associated with quite a few autoimmune conditions, including multiple sclerosis, Alzheimer’s, rheumatoid arthritis, psoriasis, and even cancer [36].
Medical doctors are already using citrullinated antibodies in testing to check for early stages of rheumatoid arthritis. An EBV-induced citrullinated peptide called VCP2 (derived from the EBV-encoded protein EBNA-2) produces anti-VCP2 IgG antibody associated with erosive rheumatoid arthritis. In a study involving 100 RA patients and 306 healthy controls, those anti-VCP2 type IgG antibodies were found in 66%, type IgM antibodies in 46%, and type IgA antibodies in 39% of people with RA, compared with less than 3% in the control group [37]. It is quite evident from research that EBV’s ability to citrullinate arginine can trigger autoimmune processes that initiate rheumatoid arthritis. More research is needed on EBV-induced citrullination and other autoimmune conditions. We will discuss dietary modulation, and the issue of arginine, in *The Recovery* section.

Since EBV is so heavily implicated in a number of autoimmune conditions, those patient cases in particular should be evaluated for CAEBV and done so in a time-sensitive manner. In other words, do not let your doctor take a back seat and wait, which is what often happens. Medical training prepares for clean-cut pathologies that then can be directed towards a pharmaceutical treatment or surgery. Instead, with autoimmune disorders, physicians tend to treat them as chronic and therefore not urgent [38], with the let’s-wait-and-see approach. If EBV takes residence in your thyroid, for example, it will continue to damage the thyroid tissue regardless of thyroid medications provided to support it if EBV is not examined as a cause and addressed. Thus, if EBV is the causative factor of a condition (and it can cause true devastation to a particular organ or organ system, and even death in extreme cases), then testing for EBV and doing so immediately is important for you regardless of your doctor’s approach. The chapter on testing for EBV is coming up shortly.

**Upper Gastrointestinal Conditions**

The involvement of EBV goes even beyond autoimmune disorders to benign upper gastrointestinal disorders such as dyspepsia (digestive
issues), duodenal ulcers, or GERD, especially with coinfections like Helicobacter pylori\textsuperscript{7} \cite{39}. We have previously discussed EBV’s ability to trigger coinfections (bacterial or viral) and other pathogens’ ability to, in turn, reactivate EBV, and H. pylori in this study by Buzas et al. may be an example of either.

The prevalence of EBV infection in dyspeptic patients is higher than in the general population, with IgG antibodies higher in patients with

\textsuperscript{7} H. pylori has also been implicated in Hashimoto’s Thyroiditis, in which case, make sure you test for both EBV and H. pylori.
duodenal ulcers than in GERD or functional dysbiosis. The prevalence of EBV in Buzas’ study’s pilot group was 70.1%, while H. pylori was 56.7% [39]. Figure 15 presents details of that study.

In addition, cases of EBV-induced severe gastritis have also been reported even though this is unusual [40] [41]. I would encourage you to work with a good functional clinician if you have dyspepsia, GERD, gastritis, or duodenal ulcer (or H. pylori). We will discuss the risk of gastric cancer and H. pylori shortly.

**Inflammatory Bowel Disease (IBD)**

A few herpesviruses, including EBV, have been suggested as causative agents of ulcerative colitis (UC) and Crohn’s disease (CD). A number of studies confirm a higher presence of EBV in the population with IBD, with cases of both UC and CD reported developing following IM, as in the case of a 20-year-old patient with prolonged IM [42].

In biopsies of 11 patients with CD, 5 with UC, 9 controls (samples of disease-free colorectal carcinoma), and 10 appendicitis samples, EBER-1 (EBV-encoded small RNA1) was found in 63.3% of CD and 60% of UC, but NOT in the other two sample groups [43]. This suggests two things: that the virus is present in both UC and CD at a similarly high level and that there is a correlation between EBV and IBD.

In a study, ileocolic resection specimens from 16 patients with UC and 20 with CD showed a higher level of EBV-infected cells in the sites of active inflammation than those of inactive inflammation in both groups, with no statistical difference between UC and CD [44], consistent with the previous study I mentioned. This reinforces the previous study, in which both UC and CD had nearly the same level of EBV RNA. What is clear here is that both forms of IBD seem to be at the same level of risk from EBV infection.

In another study, EBV (and cytomegalovirus to a lesser degree) was more prevalent in patients with IBD than in healthy controls. Mucosal viral load did not differ between inflamed and noninflamed mucosa (they
did not look at EBV-infected cells), with the conclusion made that “EBV may be more involved in the onset of IBD than in its severity and clinical evolution” [45].

In yet another study with biopsies of 58 patients with IBD, 28 were found positive and 30 negative for EBV. Interestingly, a high EBV load was more frequent in EBV-positive patients undergoing colectomy than those not undergoing colectomy (50% versus 10%). An atypical infiltrate was more frequent in EBV-positive cases (57% versus 3.3% in EBV-negative ones), with the conclusion that testing for EBV in IBD patients may be warranted. The researchers also tried a reduction of immunosuppression, which resulted in histological normalization and loss of EBV [46], which suggests that immunosuppressing medications in EBV-related cases of IBD may not be the best approach. I document in this book a strong stand for strengthening the immune system, and I also present research showing that immunosuppression can reactivate the virus, so this, I feel, is an important study.

Here is a perfect example of a greatly missed opportunity. A study analyzed EBV test results of a group with and without IBD to see if prevalence of the virus in the IBD population was higher than in the general population. The results were similar, with the wrong conclusion stating that there is no difference between the two populations [47]. The fault of the study was the markers tested and, more importantly, the markers not tested. The markers tested were:

- **CVA IgM** – This only shows for a few weeks and maximum for a few months of initial infection, and IBD may occur later as a result of chronic EBV.
- **VCA IgG** – This antibody stays with a person throughout life, so it cannot predict active status unless tested against Early Antigen IgG.
- **EBNA IgG** – This can also indicate only a past infection, unless it is tested along with EA IgG or EBNA IgM.

What was not tested:

- **EA IgG** is the most important and necessary marker for current or chronic reactivation status.
- **EBNA IgM** is rarely tested, but according to Dr. Aristo Vojdani, that positive alone can indicate current reactivation.

  My suspicion, especially based on the other studies on IBD and EBV, is that by adding EA IgG D or EBNA IgM, we might see the scale tipping towards the IBD population, especially when we consider CAEBV and the chronic character of IBD.

**EBV, the Vagus Nerve, and Gut Connection**

Before I knew anything about EBV, I was busy supporting clients with Small Intestinal Bacterial Overgrowth (SIBO), starting with Dr. Gerard Mullin’s patients at Hopkins years back. We now understand that SIBO is often a complication of gut motility impairment, with the vagus nerve being the center of attention.

The vagus nerve is the largest nerve in your body, the “wandering nerve,” starting at the base of your brain and literally wandering through the majority of your body, including your lower neck, upper thorax, muscles of larynx and esophagus, heart, lungs, and, most importantly, the whole intestinal tract, from the stomach to the anus.

The biggest implication of the vagus nerve in SIBO is small intestine dysmotility [48]. The intestinal tract relies heavily on the vagus nerve for function. Impairment in the vagus nerve in the small intestine causes weakening of the migrating motor complex (MMC), which is responsible for wave-like contractions that move foods along [49]. The impairment of MMC contributes to SIBO and chronic constipation, for example.

I have been asked a number of times if there is any connection between SIBO and CAEBV, and it is a good question because I am noticing that quite a few of my EBV clients also suffer from SIBO or vice versa. While there is not a single study on connection between the two conditions, let me show you why I think there is. Not only that, the vagus nerve damage from EBV may be another factor behind chronic fatigue syndrome and even fibromyalgia. Let’s take a closer look.

**Vagus Nerve Infection Hypothesis (VNIH)** for chronic fatigue syndrome proposed by Michael VanElzakker makes the connection to EBV
infection possible and logical [50]. VanElzakker, a Tufts neuroscientist, suggests that as the vagus nerve “wanders” through the preferred EBV’s locations like esophagus, spleen, lungs, or stomach, it will eventually come in contact with the localized EBV infection (and other herpes viruses for that matter).

He claims that reactivated EBV moves outside the nerves. Our immune cells of the nervous system called glial cells (or astrocytes) see the virus and try to digest it. Just in the previous chapter, we discussed glial cells in the context of EBV causing the breakdown of the brain blood barrier (BBB), infecting the brain, and causing the glial cells to be activated in the brain as well. Here, in the vagus nerve, glial cells have the job of protecting the vagus nerve. The problem with those glial cells is that, when activated, they produce highly inflammatory and neurotoxic compounds: interleukins 1B and 6, Tumor Necrotic Factor-a, glutamate, prostaglandins, nitric oxide, and free radicals. This in turn will fuel more viral infection. Finally, VanElzakker claims that the vagus nerve receptors tell the brain about the infection, which then causes the shutdown of the body by sending signals like fatigue, flu-like symptoms, pain, etc. The body is told to slow down and stop processing, eating, thinking, etc.

According to this hypothesis, EBV can cause localized immune system activation around the vagus nerve, and, since it is localized, it will not show positive in blood work and will be missed in medical practice.

As the glial cells release their chemicals in the dorsal horn of the spinal cord, this can also cause an increase in pain sensitivity. As this excitation of glial cells continues, eventually this pain spirals instead of shutting down. The pain response can become “pathological,” VanElzakker says, and even the slightest touch will cause pain. Why would it be different from shingles, another herpesvirus, which causes chronic pain when infecting the trigeminal nerve? Animal studies do show that infection of the vagus nerve causes fatigue and flu-like symptoms, while it does not when the vagus nerve is cut off.

VanElzakker may just be right that the vagus nerve can be infected
by herpesviruses like EBV, causing chronic fatigue and/or fibromyalgia/allodynia. On the other end of the spectrum, pathogenic infections like EBV may impair the vagal nerve function, shutting down MMCs and contributing to dysmotility that may eventually lead to SIBO. Therefore, it may be prudent to test for SIBO if your CAEBV is also causing gastrointestinal symptoms, especially constipation, but also diarrhea, alteration between constipation and diarrhea, or bloating, gas, distention, malabsorption, etc. In the meantime, VanElzakker’s hypothesis may explain why antioxidant and anti-inflammatory support is so effective in lifting my clients from their chronic fatigue.

**Neuro-Inflammation**

As I mentioned before, EBV likes to take its residence in an organ or organ system. The brain is one of them and can be severely affected by EBV; we just discussed research on MS pointing to the breach of BBB and resulting neuro-inflammation. Some of the most detrimental neurological complications of acute EBV infection reported are:

- **Encephalitis** – Brain infection [2].
- **Meningitis** – Inflammation of the meninges (can also be due to a bacterial infection) and marked by intense headache and fever, sensitivity to light, and muscular rigidity, leading (in severe cases) to convulsions, delirium, and death [2].
- **Acute Disseminated Encephalomyelitis (ADEM)** is characterized by a brief but widespread attack of inflammation in the brain and spinal cord that damages myelin, the protective covering of nerve fibers. ADEM can also be caused by bacterial infections, or less often, vaccination for measles, mumps, or rubella [2].
- **Cerebellitis** – Inflammation of cerebellum; this can lead to post-viral cerebellar ataxia (loss of control of body’s movements, such as an uneven walk) [2].

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8 **Meninges** are the three membranes (dura mater, arachnoid, and pia mater) that line the skull and vertebral canal and enclose the brain and spinal cord.

9 **Cerebellum** is the part of the brain at the back of your skull which coordinates and regulates your muscular activity.
• **Myelitis** – Inflammation of the spinal cord [2].
• **Cerebellar ataxia** – An acute case has been reported in a 28-year-old with Infectious Mononucleosis [51].

All of these are forms of brain inflammation and can be very dangerous. If you suspect that your brain is inflamed, bring this to your doctor’s attention right away for testing. The single most common complaint I hear from pretty much all my EBV clients is brain fog, sometimes severe, so just because you have brain fog does not mean that you have one of these severe conditions. Even severe brain fog can usually be cleared pretty fast with the antiviral nutritional protocol and better glucose management, which you will learn about in *The Recovery* section. However, if you have any additional symptoms listed above related to the brain, you should definitely bring this to your doctor’s attention.

**Documented Types of Cancer**

It does not get better: EBV is well studied to be “oncogenic” (causing tumor development) when the infected B cells proceed unimpeded, acquire oncogenic mutations, and become neoplastic [66]. EBV is already well documented to cause certain types of cancer and tumors (or be associated with them). An estimated 15% of global cancer burden can be linked to oncogenic tumor viruses [67].

• **Hodgkin Lymphoma** [52]
• **Burkitt’s Lymphoma** [52]
• **Pediatric Hodgkin’s Lymphoma** [53]
• **Cutaneous Lymphoma** [54]
• **Non-Hodgkin’s Lymphoma** [55]
• **Nasopharyngeal Carcinoma** [56]
• **Post-Transplant Lymphoproliferative Disorder** [57]
• **Gastric Lymphoepithelial Carcinoma** [58]
• **B cell, NK/T Cell Tumors or Lymphoma** [58]
• **Stomach Cancer** – EBV can spread to the stomach from nasopharynx, entering epithelial cells of the stomach apparently
without need of receptors [59]. Stomach cancer is of particular concern because it is the third leading cause of cancer-related death worldwide [60], and up to 18% [75] of all gastric carcinoma cases is EBV-associated. Gastric cancer incidence increases further if EBV coinfects a person along with H. pylori [60]. Thus, if your doctor has been concerned with a potential stomach cancer, you should request testing for both EBV and H. pylori. This is yet another reminder that EBV can cause reactivation of other pathogens, while other viral or bacterial infections, including H. pylori,\textsuperscript{10} can also trigger EBV reactivation, a perfect storm. Clearly, from the studies on EBV and H. pylori we have looked at, a person with H. pylori that is not improving should also be tested for EBV.

- \textbf{Angioimmunoblastic T cell Lymphoma} [61]
- \textbf{Leiomyosarcoma} – a smooth muscle tumor [59]
- \textbf{Papillary Thyroid Carcinoma}, especially in younger population studied [62]
- \textbf{Malignant Lymphoma of the Thyroid} [63]

Based on the research so far, it appears that different varieties of EBV strains are responsible for inducing a particular type of tumor [64]. More importantly, the risk of EBV-induced tumor growth may be possible without the necessity of carrying the viral DNA and without establishing a chronic infection [65]. What exactly does that mean? It could mean that just having past infection and a lingering latent stage with infected immortalized B cells might be enough to induce the tumor growth.

**More Common Types of Cancer: Colorectal and Breast**

What if oncogenic EBV also contributes to more common types of cancer such as colorectal or breast cancer? Let’s look at colon cancer. In one study, 52% of 44 colon cancer samples contained genomic DNA fragments of EBV versus 0% of other viruses tested in the same samples [68]. While that looks promising, other studies either do not show statistical significance

\textsuperscript{10} \textit{H. pylori} testing can be done through a breath test, upper endoscopy with biopsy, blood test, or stool test. No test alone is ideal, and biopsy in particular can miss \textit{H. pylori} as it grows in patches.
of EBV in this cancer or show mixed results. One thing to remember is that ulcerative colitis increases the risk of colorectal cancer, and we just discussed a few studies consistently suggesting a 60% possibility of EBV being involved in its etiology. This may be one of the connections, but more research on colorectal cancer is needed.

Let’s move on to breast cancer. Scientists have apparently known for a long time about EBV’s link to breast cancer. Studies on breast cancer have both confirming and negative results, but researchers point out that the latter may be due to detection technique issues, proteins analyzed, and variation in EBV infections or cancer itself [59]. In a study, a sample of 100 primary invasive breast carcinomas showed evidence of EBV genome by PCR (polymerase chain reaction—testing that looks for DNA of the virus) in 51% of the tumors. “The virus was restricted to tumor cells and was more frequently associated with the most aggressive tumors” [69]. In a more recent study from 2017, EBV-encoded RNA was detected in breast tumor cells in 30.1% of the samples, and those samples were statistically associated with larger tumor size [70]. Research suggests that an EBV infection may leave genetic scars and change the metabolism of some breast cells, and it is possible that over years these subtle changes may contribute to the formation of cancer [71].

The combined burden of death in 2010 from all EBV-attributable malignancies was about 143,000 individuals, which is expected to be actually higher [72]. I have no doubt that future research will prove more connections between EBV and even more types of cancer. My advice is that if you have any history of cancer, and you are of poor health, it may be prudent to test for EBV.

**Ongoing Laundry List . . . To Be Continued**

We have seen that EBV is implicated in autoimmune disorders, neuro-inflammation, and many types of cancers, but the laundry list of associated conditions is not exhausted by any means; future studies will no doubt reveal more connections. Here are more examples of other medical conditions:
• **Genital Ulcers** [73] – According to a study from 2007, only 13 instances of genital ulceration in females attributable to Epstein-Barr Virus infection had been reported by then, all caused by acute mononucleosis [74].

• **Oral and Mucocutaneous Ulcers** [75]

• **Acute Hepatitis** [76]

• **Acalculous Cholecystitis** – Inflammation of gallbladder; a rare complication of primary EBV infection [77].

• **Guillain-Barre Syndrome** (GBS) – This is a condition that causes weakness and tingling in feet and legs that spreads to the upper body causing paralysis due to nerve damage. While commonly both EBV and cytomegalovirus have been associated with this syndrome, and the latter is considered a prerequisite, there is evidence that the causative factor is not cytomegalovirus but EBV alone, and cases of EBV-induced GBS date back to the 1940s [78], as is the case of a teenage female patient who developed it following infectious mononucleosis [79], and the case of a 25-year-old [78]. EBV reactivation can also cause this syndrome after nonmyeloablative stem cell transplantation [80].

• **Idiopathic Thrombocytopenic Purpura** (ITP) is a bleeding disorder in which the immune system destroys platelets, which are necessary for normal blood clotting. People with the disease have too few platelets in the blood. EBV is a known cause of ITP [81]: ITP is considered a complication of EBV infection [82].

• **Ocular diseases associated with EBV** – These include oculoglandular syndrome, conjunctivitis (pink eye), dry eye, keratitis (inflammation of the cornea), uveitis (inflammation of the uvea), choroiditis, retinitis, papillitis, and ophthalmoplegia [83].

• **Psoriasis** – This includes both Generalized Pustular Psoriasis, which is associated with EBV [84], and Guttate Psoriasis [85].

• **Polymyositis** is a type of chronic inflammation of the muscles and is associated with EBV [86]; while polymyositis and dermatomyositis are associated with EBV, they also carry a high
risk of nasopharyngeal carcinoma in Asian countries [87], and we already documented that this carcinoma is caused by EBV.

**Complicating Co-Existing Conditions**

Another complication of having EBV is that it may affect other conditions you may also have, making things really complicated for you and your doctor. What we see in research is that EBV infection may prevent other medical conditions from resolving. For example, a recent study analyzed celiacs (people with autoimmune reactivity to gluten) that continued experiencing mucosal damage (refractory celiac disease, or RCD) despite being on a gluten-free diet. In a group of 17 RCD and 24 uncomplicated celiacs (UC), only 4 out of 24 UC had positive EBV antibodies (16.6%), while 12 out of 17 RCD (70.5%) were positive. When the EBV antibodies were analyzed further, an analysis of latency- and replication-associated proteins confirmed active infections [88].

If you know that you have celiac and you struggle with any of the conditions mentioned before while being meticulously gluten free, consider testing for EBV. It may be prudent to eliminate gluten in general to support healing, even without celiac, and we will discuss gluten more in *The Recovery*. We also just discussed a new study (published two days ago as of this writing) that is the first instance I have seen claiming that celiac can be triggered by EBV through its ability to affect regulatory genes associated with autoimmune disorders. So now we can look at EBV impacting your ability to heal from celiac, but even worse, we may expect that some cases of celiac may actually be triggered by the virus. That is a serious game changer.

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11 Celiac diagnosis is complicated. The golden standard is upper endoscopy with biopsy of small intestine, looking for villi damage. Dr. Fasano, MD, the world expert on celiac, warns that biopsy can miss damage in ileum (too deep for endoscopy) and celiacs may have no gut damage but dermatitis, infertility, early osteoporosis, or ataxia. Blood tests are not reliable alone either, since they require gluten ingestion for the antibodies to flare positive for gluten—do NOT eat gluten just for the test! Instead, work with an experienced clinical functional nutritionist to cross that bridge or do genetic testing with Enterolab.
Mimicking Other Conditions and Documented Misdiagnoses

EBV mimicking other medical conditions makes it particularly challenging to clinicians. For example, while we have just discussed EBV as one of potential causative factors in inflammatory bowel disease, it can also mimic both ulcerative colitis (UC) and Crohn’s disease (CD). Here is an example of EBV infection being misdiagnosed as CD:

EBV-associated T-cell LPD with primary gastrointestinal tract involvement can manifest as multiple discrete ulcers of the small and/or large bowel that are similar to the lesions found in CD or intestinal tuberculosis. However, when patients have multiple intestinal ulcers that are not typical of CD or intestinal tuberculosis and the clinical course is unusual, clinicians should consider the possibility of EBV-associated LPD that involves the gastrointestinal tract because the treatment strategy and prognosis are completely different. [89]

Here is an example of EBV mimicking UC: Cases of EBV-associated colitis have been reported with symptoms matching UC including lower abdominal bloating and loose, bloody, mucoid bowel movements [90].

Myositis is another opportunity for misdiagnosis. Myositis is an inflammation and degeneration of muscle tissue. Research suggests that patients with steroid non-responsive chronic progressive generalized myositis, in particular with lingual or orbital involvement, should be evaluated for CAEBV instead [91].

EBV infection (along with cytomegalovirus) can be misdiagnosed as Lyme disease [92] ... although there has been some evidence of the opposite being possible as well. This is of particular gravity because Lyme remains one of the most challenging refractory chronic conditions to treat to date, and many clinicians believe we have a Lyme epidemic.
If EBV has been shown to cause false-positives in Lyme disease tests, patients may be put on strong, long-term antibiotic therapies, decimating the existing microbiome, thus inducing dysbiosis and further weakening the immune system, which as we know, could actually trigger more EBV reactivation (beneficial bacteria in your gut are an important part of your immune system). There is no research at this time on how prevalent this misdiagnosis is, so it is unknown what percentage of these cases could actually be EBV infections. If you have been diagnosed with Lyme disease, put on countless antibiotics, and have not improved, it is important that you are tested for EBV.

“Idiopathic” Conditions

Let’s return to the medical concept of an idiopathic condition, which means a disease that arises spontaneously or the cause of which is unknown. Can idiopathic conditions be suspects for CAEBV? The answer is yes. More and more researchers warn that CAEBV and SCAEBV should be considered in these idiopathic cases [2]. The potential of CAEBV in chronically ill patients and mystery cases is high and should be seriously considered. Consistent with research, as I mentioned before, I have been asking all my new clients to test for EBV before we even start working together. It has been helpful in finding EBV cases. I urge clinicians to do the same, and you as a patient to demand it.
Here is your cheat sheet of what we have just covered—a perfect list to hand to your doctor.

<table>
<thead>
<tr>
<th>Type of EBV Involvement</th>
<th>Examples of Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misdiagnosis/ Mimicking</td>
<td>Crohn’s Disease [95]</td>
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<tr>
<td></td>
<td>Lyme Disease [98]</td>
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<tr>
<td></td>
<td>Myositis [97]</td>
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<td></td>
<td>Ulcerative Colitis [96]</td>
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<tr>
<td>Autoimmune Disorders</td>
<td>Atherosclerosis [19]</td>
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<td></td>
<td>Autoimmune Hepatitis [10] [14]</td>
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<td></td>
<td>Celiac – see under Gastrointestinal</td>
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<tr>
<td></td>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [25]</td>
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<tr>
<td></td>
<td>Chronic Fatigue Syndrome [2]</td>
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<tr>
<td></td>
<td>Dermatomyositis [87]</td>
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<td></td>
<td>Diabetes Type 1 [22] [26] [27] [28]</td>
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<td></td>
<td>Glomerulonephritis [31] [32]</td>
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<tr>
<td></td>
<td>Guillian-Barre Syndrome [78] [79]</td>
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<td></td>
<td>Guttate Psoriasis [85]</td>
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<td></td>
<td>Hashimoto’s Thyroiditis [2] [9] [12]</td>
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<tr>
<td></td>
<td>IBD (both Crohn’s and Ulcerative Colitis) – see under Gastrointestinal</td>
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<td></td>
<td>Idiopathic Thrombocytopenic Purpura [81] [82]</td>
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<td></td>
<td>Juvenile Idiopathic Arthritis [21] [22]</td>
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<tr>
<td></td>
<td>Mixed Connective Tissue Disease [23] [24]</td>
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<tr>
<td></td>
<td>Polymyositis [87]</td>
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<td></td>
<td>Psoriasis: Generalized Pustular Psoriasis – association [84]</td>
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<td></td>
<td>Rheumatoid Arthritis [16] [17] [22]</td>
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<td></td>
<td>Scleroderma [29] [30]</td>
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<td></td>
<td>Sjogren’s [13]</td>
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<td></td>
<td>Systemic Lupus [10] [15] [22]</td>
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<tr>
<td>Brain-Related</td>
<td>Acute Disseminated Encephalomyelitis [2]</td>
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<td>Cerebellar Ataxia [51]</td>
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<td></td>
<td>Cerebellitis [2]</td>
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<td></td>
<td>Encephalitis [2]</td>
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<td>Meningitis [2]</td>
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<td></td>
<td>Myelitis [2]</td>
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<td>Parkinson’s Disease - hypothesis [8]</td>
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<tr>
<th>Cancer</th>
<th>Angioimmunoblastic T-cell Lymphoma [61]</th>
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<tr>
<td></td>
<td>B cell, NK/T Cell Tumors or Lymphoma</td>
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<tr>
<td></td>
<td>Breast Cancer [70] [71]</td>
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<td></td>
<td>Burkitt’s Lymphoma [52]</td>
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<td></td>
<td>Colorectal Cancer [68]</td>
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<td></td>
<td>Cutaneous Lymphoma [54]</td>
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<td></td>
<td>Gastric Lymphoepithelial Carcinoma [58]</td>
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<td>Hodgkin Lymphoma [52]</td>
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<td></td>
<td>Leiomyosarcoma [59]</td>
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<td>Malignant Lymphoma of the Thyroid [63]</td>
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<td></td>
<td>Nasopharyngeal Carcinoma [56]</td>
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<td></td>
<td>Non-Hogkin’s Lymphoma [55]</td>
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<td></td>
<td>Papillary Thyroid Carcinoma [62]</td>
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<td></td>
<td>Post-Transplant Lymphoproliferative Disorder [57]</td>
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<td></td>
<td>Stomach cancer [59] [75]</td>
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<tr>
<th>Gastrointestinal</th>
<th>Celiac [22] [88]</th>
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<tr>
<td></td>
<td>Dyspepsia, Duodenal Ulcer, or GERD, especially with co-infections like H. pylori [39] [40] [41]</td>
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<tr>
<td></td>
<td>Inflammatory Bowel Disease (both UC and CD) [42] [43] [44] [45] [46]</td>
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<tr>
<th>Other</th>
<th>Acute Hepatitis [76]</th>
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<td></td>
<td>Acalculous Cholecystitis [77]</td>
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<td>Genital Ulcers [73]</td>
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<td></td>
<td>Ocular: oculoglandular syndrome, conjunctivitis, dry eye, keratitis, uveitis, choroiditis, retinitis, papillitis, ophthalmoplegia [83]</td>
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<tr>
<td></td>
<td>Oral and Mucocutaneous Ulcers [75]</td>
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</tbody>
</table>

Figure 16. Summary of medical conditions and EBV involvement.
Chapter 3. This Emperor Wears Many Clothes: Do You Have CAEBV?