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Role of Anti-EBNA-1 Antibodies in Psoriasis: A Seroprevalence Study

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How To Cite: Ntavari, N.; Patrikiou, E.; Gkoutzourelas, A.; et al. Role of Anti-EBNA-1 Antibodies in Psoriasis: A Seroprevalence Study. *Journal of Mosaic of Autoimmunity* **2026**, *2*(1), 5. https://doi.org/10.53941/jmai.2026.100005

Received: 23 February 2026
Revised: 21 March 2026
Accepted: 23 March 2026
Published: 30 March 2026

Abstract: Environmental triggers, particularly viral infections such as Epstein-Barr virus (EBV), may significantly contribute to the induction or exacerbation of psoriasis (Ps). EBV persists lifelong and is linked to several autoimmune diseases. Nuclear antigen 1 (EBNA-1) helps maintain latency and is a key immune target. **Objective**: This study aimed to investigate the potential association between EBV infection, specifically the humoral immune response to EBNA-1, and psoriasis by comparing seroprevalence and antibody levels in psoriatic patients versus healthy controls. **Methods**: A case-control study was conducted involving 23 patients with psoriasis (Ps) and 22 healthy controls (HC). Serum samples were analyzed for the presence of anti-EBNA-1 IgG antibodies using a standard enzyme-linked immunosorbent assay (ELISA). Seropositivity rates were compared using Fisher's Exact Test, and quantitative antibody levels, expressed as mean ± standard deviation, were compared using an appropriate parametric test. **Results**: A significantly higher proportion of psoriatic patients were seropositive for anti-EBNA-1 antibodies than healthy controls (95.7% vs. 59.1%, p = 0.004). However, among seropositive individuals, the mean quantitative antibody levels did not differ significantly between the two groups (Ps: 63 ± 25.7 vs. HC: 75.6 ± 31.6, p = ns). **Conclusion**: Anti-EBNA-1 EBV antibodies are more prevalent in psoriasis compared to healthy controls, and further research is warranted to elucidate the mechanistic role of that viral antigen as a potential contributor to disease-related immune inflammation.

Keywords: epstein-barr virus; EBNA-1; seroprevalence; autoimmunity; viral trigger

1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder characterized by hyperproliferation of keratinocytes and dysfunctional differentiation, leading to the formation of scaly, erythematous plaques. Its pathogenesis is multifactorial, involving a complex interplay of genetic predisposition, environmental triggers, and dysregulated innate and adaptive immune responses [1]. While numerous cytokines, particularly from the IL-23/Th17 axis, are known to be central drivers of the disease, the initial environmental factors that precipitate or exacerbate the condition in genetically susceptible individuals remain a key area of investigation [2,3].

Among the potential environmental triggers, infectious agents, particularly viruses, have long been suspected. The Epstein-Barr virus (EBV), a gammaherpesvirus, infects over 90% of the adult population worldwide and establishes a permanent latent infection primarily in B lymphocytes [4]. EBV is associated with a spectrum of diseases, from infectious mononucleosis to various malignancies such as Hodgkin's lymphoma and nasopharyngeal carcinoma. Notably, a growing body of evidence has also linked EBV to several autoimmune

diseases, including systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis, to name a few [5,6]. The proposed mechanisms include molecular mimicry, wherein viral antigens cross-react with self-antigens, and bystander activation of autoreactive T cells during the immune response to the virus [5,7,8].

A critical viral protein during latency is the Epstein-Barr nuclear antigen 1 (EBNA-1), which is essential for the replication and maintenance of the viral episome in host cells. EBNA-1 is a dominant target for the host's cytotoxic T-cell and humoral antibody responses [9]. The presence of anti-EBNA-1 antibodies is a standard marker of past EBV infection.

Considering the established associations between Epstein-Barr Virus (EBV) and other chronic inflammatory conditions, we hypothesized that EBV infection may also be correlated with psoriasis. If this hypothesis is accurate, a higher prevalence of EBV-specific antibodies, such as those directed against EBNA-1, would be expected to be more prominent in patients with psoriasis compared to healthy individuals. Similarly, the magnitude of anti-EBNA-1 antibodies may be elevated in patients with this disease compared with healthy controls. This study was conducted to quantitatively compare the seroprevalence and titers of anti-EBNA-1 antibodies between a cohort of patients diagnosed with psoriasis and a demographically matched healthy control (HC) group, aiming to elucidate this potential immunological association.

2. Methods

2.1. Study Population

A case-control study was approved by the institutional review board. Twenty-three (23) adult patients with a confirmed diagnosis of chronic plaque psoriasis (Ps group) were recruited from the dermatology outpatient clinic. Twenty-two (22) demographically matched HCs (mean age of PS patients vs. HCs: 51.7 vs. 48.1 years, respectively, $p = 0.375$). with no personal or family history of psoriasis or autoimmune diseases were enrolled as the control group (HC group). All participants provided written informed consent. The project has been granted an Ethics Committee approval by the Scientific & Ethics Committee of the University General Hospital of Larissa, University of Thessaly, Larissa, Greece.

2.2. Serological Analysis

Peripheral blood samples were collected from all participants. Serum was separated by centrifugation and stored at −80 °C until analysis. The presence and quantity of anti-EBNA-1 IgG antibodies were determined using a commercially available, semiquantitative line immunoassay, according to the manufacturer's instructions (Euroimmun, Lubeck, Germany).

2.3. Statistical Analysis

Statistical analysis was performed using SPSS software (version_29.0.0). Categorical data (seropositivity rates) are presented as numbers and percentages (*N*, %) and were compared between the Ps and HC groups using Fisher's Exact Test due to the sample size. Continuous data (quantitative antibody levels) are presented as mean ± standard deviation (mean ± SD). Differences in antibody levels between the two groups were analyzed using an independent samples t-test, as the normality of the antibody level distribution was found. A two-tailed *p*-value of <0.05 was considered statistically significant.

3. Results

The seroprevalence of anti-EBNA-1 antibodies was significantly higher in the psoriasis group compared to the healthy control group (Table 1). Among the 23 psoriatic patients, 22 (95.7%) tested positive for anti-EBNA-1 IgG. In contrast, only 13 of the 22 healthy controls (59.1%) were seropositive. This difference was highly statistically significant ($p = 0.004$, Fisher's exact test).

Table 1. Prevalence (positivity) and magnitude of anti-EBNA-1 antibodies in patients with psoriasis (Ps) and healthy controls (HC).

Anti-EBNA Antibody Reactivity	PS	HC	*p*
Anti-EBNA positivity (*n*,%)	22 (95.7%)	13 (59.1%)	**0.004** *
Magnitudes of anti-EBNA antibody (mean±SD) levels (AU)	63±25.7	75.6±31.6	Ns **

* Fisher's Test; ** *t*-Test.

However, when analyzing the quantitative levels of anti-EBNA-1 antibodies among those who were seropositive, no significant difference was found between the groups (*t*-Test, Figure 1). In particular, the mean antibody level in the psoriatic patient group was 63 ± 25.7 units, compared to 75.6 ± 31.6 units in the healthy control group (p = ns).

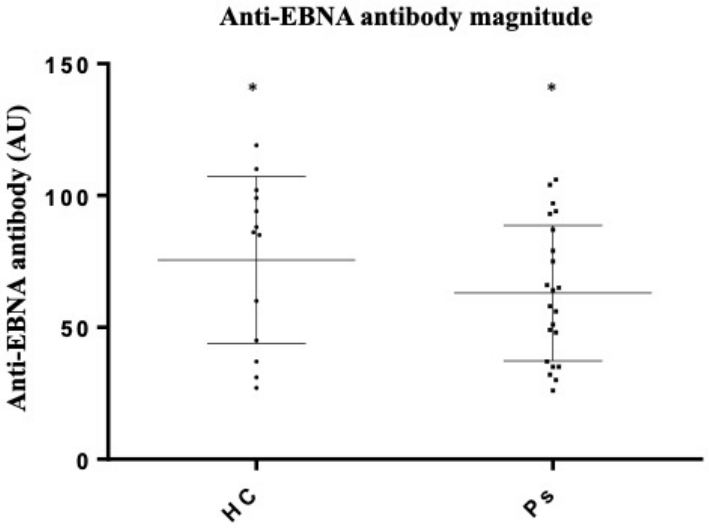

Figure 1. Anti-EBNA antibody levels in patients with psoriasis (Ps) and healthy controls (HC). Magnitude of anti-EBNA-1 antibodies in Ps patients and healthy HCs did not differ (* NS, non significant) between the two groups.

4. Discussion

EBV, also known as human herpesvirus 4, is a DNA virus that causes infectious mononucleosis in young adults, primarily targeting B cells [10]. This study demonstrates a strikingly high seroprevalence of anti-EBNA-1 antibodies in patients with psoriasis compared to healthy controls, a difference that is highly statistically significant (p = 0.004). This finding strongly suggests an association between prior infection with EBV and psoriasis. The near-universal seropositivity in the psoriatic cohort approaches the rate observed in classic EBV-associated diseases such as multiple sclerosis and systemic lupus erythematosus [5,11], suggesting that EBV may be a key environmental trigger in psoriatic disease. Several reasons may explain the observed results, including the relatively low prevalence of anti-EBNA antibodies in healthy controls (59.1%), such as potential methodological or sampling issues. Differences in EBNA serology do not immediately correlate with serology for other EBV antigens, which are more universally present. That could explain the observed lower reactivity against EBNA noted in HCs. Sampling bias or other sampling issues are unlikely because both cohorts were demographically matched. Line immunoassays, whether qualitative or semi-quantitative, do not allow precise measurements compared with other assays such as ELISA, and this limitation must be acknowledged.

The most straightforward interpretation of our data is that latent EBV infection constitutes a significant risk factor for the development of psoriasis; however, this remains highly hypothetical, as there are no direct epidemiological studies to substantiate this assertion. Several mechanisms may explain EBV's role in Ps; EBV-infected B cells can present antigens and produce cytokines that may steer the immune response toward a Th1/Th17 phenotype, which is key to psoriasis development [5]. Acute guttate psoriasis in a 15-year-old girl with EBV infection has been documented [12]. Also, other case reports suggest an association between infection and the onset or exacerbation of psoriasis, with evidence primarily from observational studies [13,14].

EBNA-1 has been shown to share amino acid sequence similarities with various human proteins, including those involved in the pathogenesis of multiple sclerosis [7,8,15]. It is plausible that T cells or antibodies initially primed to fight EBNA-1 could cross-react with a yet-unidentified self-antigen in the skin, triggering the inflammatory cascade seen in psoriasis, similar to that noted in systemic lupus erythematosus [16]. EBNA-1 is predominantly engaged in the virus's latent phase and is essential for genome replication and modulation of host cellular functions. The constant, low-level antigenic stimulation from the latent virus could lead to a state of chronic, nonspecific immune activation, lowering the threshold for the development of autoimmune disorders such as psoriasis. Few other mechanisms have been elucidated, but hypotheses include EBV DNA influencing Th17 cells via Toll-like receptor 9, leading to IL-17 secretion [17]. Ohta et al., for example, found increased Th17 cells

and IL-17 production in chronic EBV infection, with IL-17 being central to psoriasis pathogenesis. Thus, elevated Th17 levels and IL-17 may thus be key mechanisms by which EBV triggers or worsens psoriasis [18].

The second key finding—that there is no significant difference in the quantitative level of anti-EBNA-1 antibodies between psoriatic patients and healthy controls—is equally important. It indicates that the association is not driven by a more robust or active humoral immune response to EBNA-1 in psoriasis patients. Instead, it suggests that the mere presence of the virus and the subsequent initiation of a sustained immune response against it (seropositivity) may be the critical factor. This is reminiscent of the "hit-and-run" hypothesis, where the initial viral infection causes permanent dysregulation of the immune system, leading to autoimmunity, without requiring ongoing high-level viral replication or a massive antibody response [19].

The limitations of the study are numerous: it is constrained by its case-control design, which can indicate an association but not establish causality. The sample size, although adequate to demonstrate a significant difference in seroprevalence, remains relatively small. Additionally, antibodies were measured against only a single EBV antigen (EBNA-1). Future prospective cohort studies with larger sample sizes are essential to validate these findings. Moreover, subsequent research should encompass a broader panel of EBV serological markers and antigens (e.g., anti-VCA, anti-EA) to more accurately characterize the nature of EBV infection (e.g., recent reactivation versus long-term latency). Most critically, mechanistic investigations are necessary to elucidate the pathophysiological connection, such as examining cross-reactivity between EBNA-1 and skin antigens or profiling T-cell responses to EBV in patients with psoriasis. Nevertheless, the present findings are interesting and worthy of mention.

5. Conclusions

Our findings provide significant serological evidence for a link between Epstein-Barr virus infection and psoriasis. The higher prevalence of anti-EBNA-1 antibodies in psoriatic patients indicates EBV as a potential environmental trigger. Whether this is due to molecular mimicry or other immunological mechanisms remains to be seen [20]. The lack of difference in antibody levels between groups emphasizes the significance of viral latency rather than response magnitude. These results support further research into the viral etiology of psoriasis and may guide future therapeutic and preventive approaches targeting viral triggers. However, this is a preliminary study. And there is currently no evidence that it is a causative agent.

Author Contributions

Experimental testing, data acquisition: N.N. and E.P.; Artwork: E.P. and A.G.; Clinical data and patient follow-up: N.N. and E.Z.; Statistical analysis: E.P.; Data interpretation: E.P., C.L. and D.P.B.; Overall Supervision: D.P.B. and E.Z.; Drafting of manuscript: D.P.B. and E.Z. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee, Faculty of Medicine, School of Health Sciences, University of Thessaly (#48/02 December 2019).

Informed Consent Statement

Written informed consent has been obtained from the patients who have participated in the study.

Data Availability Statement

The authors ensure accessibility of their data to other competent professionals upon justified request provided that the confidentiality of the participants can be protected and legal rights concerning proprietary data do not preclude their release.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Grammarly for fine grammar and syntax performance of the manuscript, as well as correction of spelling errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

EBNA-1, Epstein-Barr nuclear antigen 1; EBV, Epstein-Barr Virus; HC, healthy control; IL-17, interleukin-17; Ps, psoriasis; Th1, T helper 1; Th17, T helper 17.

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