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Epstein-Barr virus (EBV) reactivation in post COVID-19

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ABSTRACT

Objective: To determine if there is a link between prolonged COVID symptoms and the reactivation of EBV.
Methods: This study was an observational (case-control) analysis involving 140 patients who tested positive for COVID-19 and are experiencing persistent symptoms such as fatigue and post-exertional malaise. Additionally, a control group of 80 individuals, matched for age and gender, who have fully recovered from SARS-CoV-2 infection without these symptoms, was included. The research took place between December 2023 and March 2024 at Benha University Hospitals in Benha, Egypt. The reactivation of the Epstein–Barr virus (EBV) was identified by detecting EBV genetic material using TaqMan probes, along with at least one set of primers (*Bam*HI and LMP2).
Results: Initial hospitalization during acute COVID-19 infection is significantly associated with post-COVID fatigue ***(p-value 0.007*)***. No significant associations were found for risk factors like diabetes and hypertension. EBV replication observed was due to EBV reactivation rather than primary infection. EBV-specific antibody titers EBNA-1 IgG (p-value 0.004*) and EA-D IgG ***(p-value 0.008*)***. 40/140 (28.6 %) patients with COVID-19 with persistent fatigue showed EBV reactivation in contrast to 9/80 (11.3 %) of controls ***(P-value 0.003*)*** using the same detection methods.
Conclusion: EBV reactivation plays a role in Long-COVID syndrome following COVID-19 infection supporting the usage of EBV inhibitors for long-term COVID-19 treatment.

1. Background

Epstein–Barr virus (EBV) is a type of gamma herpesvirus that is primarily responsible for causing infectious mononucleosis (IM). Additionally, EBV is associated with several types of cancers, including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin's disease, T-cell lymphoma, and post-transplant lymphoproliferative disorder [1].

EBV infects over 90 % of people globally and remains dormant (latent) in >95 % of healthy adults. Its prevalence is significant across all regions worldwide. No evidence of difference in susceptibility among races [2–5].

Primary infection with Epstein-Barr virus (EBV) usually does not present any symptoms in children and adolescents. However, when EBV infection leads to infectious mononucleosis, there is a significant increase in lymphocytes. The virus can also cause persistent or recurring infections, affecting both epithelial cells and B cells. Furthermore, in many individuals, EBV can switch between active (lytic) and inactive (latent) phases [6].

Medical professionals often utilize serological tests that detect EBV viral capsid antigen (VCA) IgM or EBV early antigen-diffuse (EA-D) IgG to identify EBV reactivation. During EBV reactivation or the early phases of acute primary infection, it is common to detect EBV VCA IgM. When a persistent EBV infection progresses, however, EBV EA-D IgG is more frequently detected [7,8].

The National Institute for Health and Care Excellence defines Long-COVID as persistent symptoms lasting >12 weeks after the first infection and affects around 10 % of those infected with SARS-CoV-2 [9]. Some estimates put the percentage of COVID-19 individuals whose symptoms persist long after the disease's initial phase has passed at 30 % [10].

There is increased risk for long-COVID syndrome with more severe COVID-19 course, longer symptoms duration, and female gender [11].

While organ damage may explain some Long-COVID symptoms, such as shortness of breath or chest pain, the precise cause of post-COVID

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fatigue—characterized by severe exhaustion and difficulties with memory and concentration—remains unclear [12]. Several viruses can cause post-viral fatigue, including the influenza virus and the Epstein-Barr virus (EBV). Additionally, conditions such as myalgic encephalomyelitis/chronic fatigue syndrome—recognized by the World Health Organization as distinct illnesses—can develop after viral infections, among other possible causes [13].

We aimed to find evidence linking Long-COVID symptoms to EBV reactivation, as many symptoms of Long-COVID resemble those of EBV reactivation.

1.1. Purpose

To determine if there is a link between prolonged COVID symptoms and the reactivation of EBV.

2. Methods

This is an observational (case-control) study involving 140 COVID-19 patients who tested positive and recovered from SARS-CoV-2 acute symptoms but continued to experience symptoms such as fatigue, post-exertional malaise (PEM), and autonomic dysfunction lasting ≥28 days [14]. For comparison, 80 control patients matched by age and gender, who also recovered but did not have persistent fatigue, were recruited. All participants had mild and moderate infections. The study was conducted between December 2023 and March 2024 at Benha University Hospitals in Egypt. The study received ethical approval from the Faculty of Medicine at Benha University (REC-FOMBU) under code RC-10–11–2023 and was conducted under the Helsinki Declaration. Written informed consent was obtained from all participants.

The study included patients experiencing symptoms such as autonomic dysfunction, orthostatic intolerance, post-exertional malaise (PEM), and chronic tiredness which persisted in patients who have recovered from acute COVID-19 infection. Diagnosis of acute COVID-19 infection through medical history, clinical examinations, laboratory investigations and radiological criteria for COVID-19 infection. Patients with autoimmune diseases or immunocompromized conditions were excluded from this study.

Samples were collected both short-term (20–90 days) and long-term (>100 days) after the onset of acute SARS-CoV-2 infection in patients with Long-COVID-19.

EDTA containers were used to collect whole blood samples. To obtain plasma, these samples were centrifuged. The samples were divided into four portions for the measurement of anti-EBV antibodies and to conduct real-time PCR analysis. They were stored at −80 °C until needed.

All participants were tested for SARS-CoV-2 RNA in throat washings during the period of acute COVID-19 infection, EBV DNA in blood, using real-time PCR for EBV and real-time RT-PCR for SARS-CoV-2, and anti-EBV serological testing through Enzyme-linked immunosorbent assay (ELISA).

2.1. Quantification of EBV

Using Qiagen's DNeasy Blood & Tissue Kit, DNA was extracted from 200 µL of plasma. The TaqMan primer sets used for quantifying Epstein-Barr virus (EBV) targeted two sections of the EBV genome: BamH1W and LMP2. These primer kits were obtained from IDT [15].

The TaqMan probes used in our study are equipped with a fluorescent reporter (FAM, emitting at 520 nm) and a double quencher (ZEN/IBFQ). For the BamHIW1 region of the EBV genome, the forward primer sequence was "GCAGCCGCCCAGTCTCT" and the reverse primer sequence was "ACAGACAGTGCACAGGAGACT". The corresponding TaqMan probe sequence was "FAM-AAAAGCTGGCGCCCTTGCG-ZEN/IBFQ".

For the LMP2 region, the forward primer sequence was "AGCTGTAACTGTGGTTTCCATGAC" and the reverse primer sequence was "GCCCCCTGGCGAAGAG". The TaqMan probe sequence for LMP2 was "FAM-CTGCTGCTACTGGCTTTCGTCC TCTGG-ZEN/IBFQ".

For our quantitative PCR (qPCR) analysis, we used the QuantStudio™ 5 system from Applied Biosystems. The procedure began with an initial step where the DNA strands were separated at 95 °C for 2 min. This was followed by 45 cycles, during which the DNA was heated to 95 °C for 15 s to denature it, and then cooled to 60 °C for 1 min to allow for annealing and extension. Both positive and negative controls were included in each essay. We established a threshold cycle (CT) cutoff of 40; any samples showing results beyond this point were considered undetectable. Negative controls were expected to show no amplification signals by cycle 45. This ensured that any detected signal in samples by cycle 40 or earlier indicated levels at least 32 times higher than the background.

2.2. Anti-EBV serological testing by enzyme-linked immunosorbent assay (ELISA): EBNA-1 igg, EA-D igg, VCA igm

We used commercial ELISA kits from IBL International, Germany, to test EBV antibodies in the plasma of all participants. The antibodies examined included IgM against Viral capsid antigen (VCA), IgG against EBV nuclear antigen (EBNA-1), and IgG against EBV early antigen (EA). The assays were conducted with an average analytical sensitivity of 1.29 U/mL, following the protocols provided by the manufacturer.

2.3. Statistical analysis

All data were tabulated and then analyzed using IBM SPSS 20.0 software. We used quantitative and percentage-based representations for categorical data. To compare two datasets, we employed the chi-square test, and we utilized Fisher's exact test when the expected cell count was <5 for >20 % of the cells. The normal distribution of continuous data was assessed using the Kolmogorov-Smirnov test. We defined quantitative data using the mean, median, standard deviation, and range (from the lowest to the highest values). For comparing two groups with non-normally distributed quantitative data, we applied the Mann-Whitney test. A p-value of <0.05 was considered statistically significant.

3. Results

No significant differences were observed between the two groups regarding age and gender Table 1.

The initial hospitalization is linked to moderate Covid-19 cases present with fever, respiratory symptoms, and radiographic features specially with chronic disorders like diabetes and hypertension. No significant differences were found between the two groups regarding the prevalence of chronic disorders like diabetes and hypertension. There is

Table 1
Comparison of the two studied groups based on demographic data.

	Group A (n = 140)	Group B (n = 80)	Test of Sig.	p-value
Sex				
Male	55 (39.3 %)	33 (41.3 %)	χ^2=0.082	0.775
Female	85 (60.7 %)	47 (58.8 %)		
Age (years)				
≤45	54 (38.6 %)	39 (48.8 %)	χ^2=2.161	0.142
>45	86 (61.4 %)	41 (51.3 %)		
Mean ± SD.	47.2 ± 11.9	42.7 ± 14.3	U=	0.035*
Median (Min. – Max.)	49.5 (16.0 – 66.0)	46.5 (16.0 – 60.0)	4642.000*	

SD: Standard deviation; U: Mann Whitney test; χ^2: Chi-square test.
p: p-value for comparing the two studied groups.
*: Statistically significant at $p \leq 0.05$.

a significant correlation between both groups regarding patients hospitalization Table 2.

At the time of sampling, SARS-CoV-2 RNA was undetectable in throat washings of all study participants from both groups, as determined by real-time RT-PCR. The titers of SARS-CoV-2 antibodies (IgA and IgG) did not differ between the cohorts.

In group (A), which consisted of individuals previously infected with SARS-CoV-2 and experiencing persistent fatigue, EBV reactivation was detected in 40 out of 140 samples (28.6 %) using TaqMan probes and specific primer sets (*Bam*HI and LMP2). Conversely, in group (B), comprising individuals with prior SARS-CoV-2 infection but without persistent fatigue, only 9 out of 80 samples (11.3 %) showed reactivated EBV using the same detection methods. The EBV replication observed was due to EBV reactivation rather than primary infection. EBV-specific antibody titers EBNA-1 IgG **(p-value 0.004***) and EA-D IgG **(p-value 0.008***) Table 3.

4. Discussion

The SARS-CoV-2 virus causes respiratory illness known as COVID-19. Up to 10 % of patients develop Long-COVID, a syndrome defined by the National Institute for Health and Care Excellence as post-infectious long-term symptoms for >12 weeks, which cannot be explained by alternative pathologies [9]. In literature, many researchers pointed to link Epstein-Barr virus (EBV) reactivation in individuals who had COVID-19 infection or those experiencing Long-COVID [16–20]. The objective of this study was to explore any potential link between EBV reactivation and Long-COVID.

Although some researchers, including Almasri et al. [18] and Sudre et al. [21] found that older age is significantly linked to post-COVID-19 syndrome. Additionally, other researchers confirmed female gender is more likely to experience Long-COVID-19 [22,23], the current shows no notable differences in age and sex between the two groups, consistent with Mahmoud et al. [17].

EBV (Epstein-Barr Virus) infection triggers a series of well-documented immune responses in the body. Initially, levels of VCA-IgM antibodies rise shortly after the initial infection. About a month after the infection begins, EBNA-IgG antibodies appear, signaling a more established immune response against EBV. Additionally, EA-IgG antibodies develop during the initial infection and may increase again during periods when EBV reactivates.

Serological tests that detect these EBV-specific antibodies are commonly used to diagnose EBV infection and determine its stage. Specifically, the presence of EBV early antigen-diffuse (EA-D) IgG antibodies is a clear indicator of recent viral activity or EBV reactivation in the body [24].

EBV reactivation has also been investigated in connection with Long-COVID. According to the CDC's 2022 report, about 20 % of adults in the United States who had previous COVID-19 infections experienced Long-COVID symptoms. Between January 2020 and June 2022, Long-COVID was linked to over 3500 deaths in the United States (https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20221214.htm).). Patients hospitalized with Long-COVID commonly experience persistent symptoms such as fatigue, difficulty breathing (dyspnea), memory impairment, and sleep disturbances [25].

In a review of literature from 2021, researchers found that 66.7 % of individuals with prolonged COVID tested positive for EBV. The detection of EA-D and VCA IgM antibodies was used to determine this reactivation [27].

EBV infection status, implying that the immunological and inflammatory context generated by natural SARS-CoV-2 infection may be crucial for the reactivation of latent EBV [26]. The EBV replication observed in the current was due to EBV reactivation rather than primary infection. EBV-specific antibody titers EBNA-1 IgG **(p-value 0.004***) and EA-D IgG **(p-value 0.008***).

In group (A), 60/140 (42.9 %) patients showed anti-EBNA-1 IgG detectable levels, indicating a previous infection of EBV. Additionally, 50/140 (35.7 %) were anti-EA-D IgG positive, while only 6/140 (4.3 %) had anti-VCA IgM antibodies. In contrast, in group (B), 19/80 (18.8 %) patients had detectable anti-EBNA-1 IgG, suggesting a past EBV infection. Furthermore, 15/80 (18.75 %) were positive for anti-EA-D IgG, and only 2/ 80 (2.5 %) had anti-VCA IgM antibodies. These findings are consistent with those reported by *Bernal and Whitehurst* [16], In their research, they observed that 96/106 patients (90.56 %) had detectable levels of anti-EBNA-1 IgG, indicating a history of previous EBV infection. Additionally, 25/103 (24.3 %) patients tested positive for anti-EA-D IgG. Among the samples, 23/93 (24.7 %) showed positivity for both EBNA-1 and EA-D antibodies. Specifically, this dual positivity was found in 12/46 COVID-positive patients (26.1 %) and 11/47 COVID-negative (23.4 %) patients.

In a study, two out of forty-eight COVID-positive patients (4.2 %) tested positive for VCA antibodies, while three out of forty-eight COVID-negative patients (6.3 %) tested positive for both VCA antibodies and another factor. Additionally, according to Chen et al. [27], 55.2 % of COVID-19 patients who were hospitalized in Wuhan, China, showed evidence of EBV reactivation through VCA IgM antibodies.

Saade et al. [28] research indicated that upon their admission to the intensive care unit (ICU), 56.1 % of patients with severe COVID-19 exhibited signs of Epstein-Barr virus (EBV) reactivation. Another study found that among critically ill COVID-19 patients, there were elevated levels of antibodies against EBV, as well as detectable EBV in their plasma [29].

This study points out that initial patient hospitalization during acute COVID-19 infection is significantly associated with post-COVID fatigue **(p-value 0.007*)** coinciding with the results of Carvalho-Schneider et al. [30] and Mahmoud et al. [17] studies.

The current study shows no statistically significant association was noticed between the two groups regarding risk factors such as diabetes mellitus and hypertension mismatches with Mahmoud et al. [17]. They encountered limitations in their study related to various associated

Table 2
Comparison of the two groups studied concerning symptoms, hospitalization, and risk factors.

	Group A (n = 140)	Group B (n = 80)	χ^2	p-value
Duration of fatigue				
Long-term (>100 days)	112 (80.0 %)	–	–	–
Short term (20–90 days)	28 (20.0 %)	–		
Persistent fatigue	140 (100.0 %)	0 (0.0 %)	220.0*	**<0.001***
Hospitalization	30 (21.4 %)	6 (7.5 %)	7.217*	**0.007***
Hypertension	28 (20.0 %)	9 (11.3 %)	2.786	0.095
Diabetes	12 (8.6 %)	8 (10.0 %)	0.126	0.723

χ^2: Chi square test.
p: p value for comparing the two studied groups.
*: Statistically significant at $p \leq 0.05$.

Table 3
Comparison of the two studied groups concerning EBV genome detection using RT-PCR and antibody titers assessed by the ELISA technique.

	Group A (n = 140)	Group B (n = 80)	χ^2	p-value
EBV DNA (Real-time PCR)	40 (28.6 %)	9 (11.3 %)	8.823*	**0.003***
VCA IgM	6 (4.3 %)	2 (2.5 %)	0.463	^{FE}p=0.714
EBNA-1 IgG	60 (42.9 %)	19 (23.8 %)	8.076*	**0.004***
EA-D IgG	50 (35.7 %)	15 (18.8 %)	7.038*	**0.008***

χ^2: Chi-square test; FET: Fisher Exact test.
p: p-value for comparing the two studied groups.
*: Statistically significant at $p \leq 0.05$.

factors and had small sample sizes.

The discrepancies in literature regarding the risk factors for developing post-COVID syndrome can be attributed to significant variations in study methods, populations examined, sample sizes, and follow-up durations. Nonetheless, it is important to closely monitor individuals with diabetes for any signs of developing post-COVID syndrome [19].

The results of the current study indicate that EBV reactivation was detected in 40 out of 140 (28.6 %) Long-COVID patients. In contrast, only 9 out of 80 (11.3 %) non-Long-COVID patients showed evidence of EBV reactivation. These findings differ significantly from those reported by Rohrhofer et al. [31], who found EBV DNA in 15 out of 30 (50 %) Long-COVID patients and in only 4 out of 20 (20 %) non-Long-COVID patients who had recovered from their acute SARS-CoV-2 infection.

The findings of the current study contrast with those of Zubchenko et al. [32], who reported that 42.6 % of Long-COVID patients showed reactivation of Epstein-Barr Virus (EBV) through polymerase chain reaction (PCR) tests that identified EBV DNA in peripheral blood. This discrepancy may be explained by the different detection techniques and kits employed in the studies.

The results of this study align with the findings reported by Bernal and Whitehurst [16], which noted that EBV reactivation occurred in 27.1 % of individuals compared to 12.5 % in the COVID-negative group. Among non-Long-COVID individuals, the rate of reactivation corresponds with a 2016 study conducted at Johns Hopkins Hospital, which found a 12 % incidence of EBV reactivation in individuals without any history or current symptoms of EBV-related diseases.

The findings of this study raise the possibility of further research into the use of EBV inhibitors for long-term COVID-19 treatment. This is supported by the work of Meng et al. [33], who found that patients experiencing reactivation of EBV due to COVID-19 had improved survival outcomes when treated with ganciclovir, an EBV inhibitor.

4.1. Limitations

Our study has several limitations. For instance, HLA subtypes linked to latent EBV infection were not evaluated due to the absence of EBV sampling conducted during or before acute SARS-CoV-2 infection, interventions for COVID-19 (e.g., antiviral agents, steroids) and the severity of COVID-19 were not involved in the analysis and the sample size was small.

5. Conclusion

EBV reactivation plays a role in Long-COVID syndrome following COVID-19 infection supporting the usage of EBV inhibitors for long-term COVID-19 treatment.

Ethical approval and consent to participate

This study received ethical approval from the Ethical Committee of the Faculty of Medicine at Benha University (REC-FOMBU) in Egypt, under approval code RC-10–11–2023. It was conducted in strict accordance with the Helsinki Declaration of 1975, as amended, ensuring compliance with international ethical standards. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availabilty of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Eslam Farid Abu Shady: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Abdelhakim Fouad Ghallab:** Conceptualization, Writing – original draft, Writing – review & editing. **Doaa Abdullah Shaker:** Data curation, Writing – original draft, Writing – review & editing. **Rasha Abd Elhamid Elsayed:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare they do not have any conflict of interest.

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All authors of this research confirm their consent for publcation of this study.

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