CLINICAL AND SUBCLINICAL FEATURES, AND TREATMENT OUTCOMES OF CHILDREN WITH CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION: A RETROSPECTIVE SINGLE-CENTER ANALYSIS

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ABSTRACT

Introduction: Chronic active Epstein-Barr virus (CAEBV) is a lymphoproliferative disorder associated with EBV infection. CAEBV is a rare but severe, potentially life-threatening illness. Clinical manifestations develop in multiple organ systems and mortality. This study aims to investigate clinical, subclinical features and treatment outcomes of children with CAEBV infection. **Method:** This retrospective study was conducted over 5 years, from January 2017 to December 2021, at the Vietnam National Children's Hospital (VNCH), the country's largest referral tertiary children's hospital. Children diagnosed with CAEBV during this period were included in the study. All statistical analyses were performed using SPSS software version 20.0. **Results:** There were 43 CAEBV patients, of which 21(48.8%) showed hemophagocytic syndrome (HLH–EBV) at the time of diagnosis. The median age of onset was 41 months, the male/female ratio was 2.3/1 and 21(48.8%) patients experienced severe outcomes or death during the study period. Symptoms include fever (100%), hepatomegaly (97.6%), splenomegaly (83.4%), and lymphadenopathy (46.5%). There are changes in hematologic, biochemical tests and immune cell counts in CAEBV. The high EBV viral load in serum remained stable after receiving antiviral treatment, with a median of 2.32 x 10^5 cp/ml. **Conclusions:** Although many measures, such as antivirals, immunosuppressants, chemicals and intravenous immunoglobulin are adopted, the disease has a high mortality rate. More research is needed to clarify clinical characteristics, the roles of diagnostic tests and treatment measures for this group of patients.

Keywords: *Children, HLH, EBV, CAEBV*

I. INTRODUCTION

Chronic active Epstein-Barr virus infection is a lymphoproliferative disorder characterized by abnormal EBV antibody responses, EBV DNA and RNA presence, or proteins in tissue lymphocytes [1]. Children often illustrate with fever, lymphadenopathy, splenomegaly, hepatitis and thrombocytopenia. Furthermore, several patients have progressive immunodeficiency and surrender to opportunistic infections, hemophagocytosis, multiorgan failure or EBV-positive lymphomas [2]. CAEBV is potentially life-threatening due to appropriate diagnosis, and therapeutic interventions are essential for profitable clinical outcomes. Epidemiologically, CAEBV is mainly found in East Asia and less common in Western countries, suggesting the disease has a genetic predisposition. In Asian countries, research from Japan shows that EBV mainly infiltrates T or NK cells, while in the USA, it predominantly affects B cells [3-5]. In Vietnam, EBV studies concentrate primarily on malignancies like lymphomas or nasopharyngeal cancer, with no research on

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CAEBV. In addition, CAEBV is rare and challenging to diagnose, and there is no standardized treatment protocol globally or in Vietnam.

Moreover, there currently needs to be more consensus and a lack of evidence from pediatric CAEBV trials. Immunosuppressive therapy with Rituximab, EBV-specific T-cell therapy, and cytotoxic chemotherapy only achieves short-term remission [4,6]. Hematopoietic stem cell transplant (HSCT) is effective, especially in patients not responding to chemotherapy therapy [1,7]. Age of onset over 8 years and liver dysfunction are poor prognostic factors with complications like lymphoma, hemophagocytic lymphohistiocytosis (HLH), immunodeficiency, and infections [6]. Furthermore, patients with T cell infection by EBV had shorter survival times than patients with NK cell infection [8,9]. To address the question: "What is the current status of diagnosis and treatment of CAEBV infection in Vietnam?", we conducted this study.

II. PARTICIPANTS AND METHODS

2.1. Participants

During the study period, children between 1 month and 16 years of age diagnosed with CAEBV were enrolled. The diagnostic criteria for CAEBV are as follows: (1) Persistent or recurrent symptoms of infectious mononucleosis syndrome lasting more than 3 months, (2) Positive EBV PCR test in the serum, (3) Other causes do not explain chronic illness at the time of diagnosis. Patients diagnosed with autoimmune diseases, malignancies, congenital immunodeficiency, HIV, or other acquired immunodeficiencies were excluded [10]. Exclusion criteria: Cases where the patient's family did not agree to participate in the study were excluded. We obtained written informed consent from all participants' parents or legal guardians, and the study was approved by the Vietnam National Children's Hospital Institutional Review Board (Approval no. VNCH-TRICH-2612). The study was conducted by the Declaration of Helsinki.

2.2. Study design

This retrospective study was conducted over 5 years, from January 2017 to December 2021, at Vietnam National Children's Hospital (VNCH)—the country's largest referral tertiary children's hospital.

2.3. Data acquisition

Data on clinical and demographic characteristics, laboratory, and therapeutic variables were found within 24 hours of admission and follow-up outcome treatment. Daily data were routinely collected using standard case report forms (CRFs).

2.4. Statistical analysis

We used a convenient method for determining the sample size of our study. All statistical analyses were performed using SPSS software version 20.0. Categorical variables were described as frequencies and percentages, while continuous variables were described as the median and interquartile range (IQR). Results were described as odds ratio (OR) and 95% confidence intervals (CIs). Kaplan-Meier charts were used to represent survival probabilities over time.

III. RESULT

3.1. Baseline characteristics of the study population

A total of 43 pediatric patients meeting the diagnostic criteria for CAEBV were enrolled, including 21 who satisfied the

criteria for HLH-EBV at the onset. Among the 43 patients, there were 37 males and 16 females, with a male-to-female ratio of 2.3:1. The median age of disease onset was 41 months (ranging 10-163). Anti-EBV Antibodies: Of 43 patients, 23 were tested for at least 2 specific EBV antibodies in the serum. The results showed that all patients were negative for VCA-IgM and positive for VCA-IgG (100%). Among these, 4 out of 23 patients were positive for 3 antibodies: VCA-IgG, EA-IgG, and EBNA. One patient was negative for EA-IgG and positive for EBNA-IgG, while another patient was positive for EA-IgG and negative for EBNA.

3.2. Clinical and laboratory characteristics of CAEBV patients

Table 1: ***Clinical characteristics of patients hospitalized with CAEBV***

Characteristics	n	Proportion	Characteristics	n	Proportion
Fever	43	100	Pharyngeal ulcers	2	4.7
Hepatomegaly	42	97.6	Coronary artery dilatation	4	9.3
Splenomegaly	36	83.4	Brain lesions	4	9.3
Lymphadenopathy	20	46.5	Proteinuria	4	9.3
Pulmonary lesions	19	44.2	Skin lesions	2	4.7
Gastrointestinal lesions	13	30.2	External genital infiltration	1	2.3

Values are given as n (%)

Common symptoms: fever (100%), hepatomegaly (97.6%), splenomegaly (83.4%), lymphadenopathy (46.5%), lung lesions (44.2%), gastrointestinal lesions (30.2%), coronary artery dilation (9.3%), neurological damage (9.3%), kidney lesions (9.3%), skin lesions (4.7%), genital lesions (2.3%).

Table 2: ***Subclinical characteristics of patients hospitalized with CAEBV***

Paraclinical findings		n		
			N	Proportion
Haematology	WBC < 4 10^9/L	43	28	65.1
	Hemoglobin < 100 g/l	43	31	72.1
	Platelets < 100 10^9/L	43	24	55.8
Blood biochemistry	GOT > 40	43	38	88.4
	GPT > 40	43	24	55.8
	Albumin < 35 g/l	43	33	76.7
	LDH > 240	27	27	100
	Ferritin > 500	40	32	80
	Triglyceride > 3 mmol/l	39	31	79.5
Coagulation profile	PT > 15s	43	13	30.2
	APTT > 45s	43	2	4.65
	Fibrinogen < 1.5 g/l	43	10	23.25
Bone marrow cell count	Increase > 100 10^9/L	42	3	7.1
	Normal 30 – 100 10^9/L	42	12	28.6
	Decrease < 30 10^9/L	42	27	64.3

Values are given as N (%)

Definition of abbreviation: WBC: white blood count, PT: Prothrombin time, aPTT: activated partial thromboplastin time, LDH: Lactate dehydrogenase, GOT: glutamate oxaloacetate transaminase, GPT: glutamyl pyruvic transaminase.

Blood tests predominantly demonstrate pancytopenia secondary to bone marrow hypoplasia.

Table 3: ***Cellular and humoral immunity results in CAEBV***

Immunity			n	Proportion
Cellular immunity	%CD3	Normal	9	40.9
		Decrease	7	31.8
		Increase	6	27.3
	%CD4	Normal	7	31.8
		Decrease	11	50
		Increase	4	18.2
	%CD8	Normal	10	45.4
		Decrease	4	18.2
		Increase	8	36.4
	%CD19	Normal	10	45.5
		Decrease	12	54.5
		Increase	0	0
	%CD56	Normal	8	36.4
		Decrease	6	27.3
		Increase	8	36.4
Humoral Immunity	IgG	Increase	10	45.5
		Normal	12	54.5
	IgE	Increase	5	62.5
		Normal	3	37.5

Values are given as n (%), CD: Cluster of Differentiation, Ig: Immunoglobulin

Immune dysregulation was demonstrated by lymphopenia ($CD3^+$, $CD19^+$), $CD4^+/CD8^+$ ratio imbalance, $CD56^+$ (NK cell) alteration, and increased IgG and IgE levels.

3.3. Therapeutic interventions and treatment outcomes

3.3.1. Therapeutic interventions for patients hospitalized with CAEBV

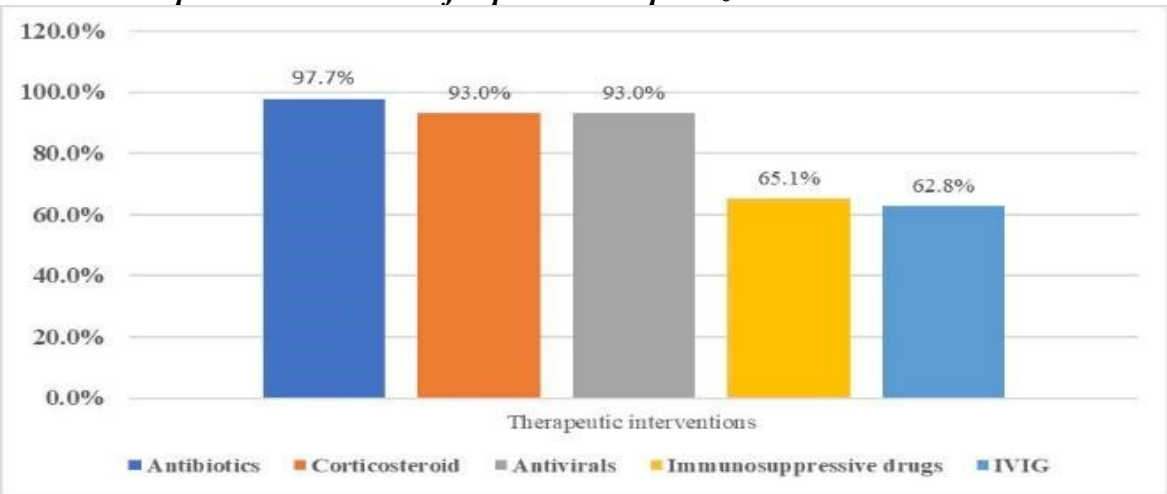

Figure 1: ***Therapeutic interventions applied in CAEBV***

IVIG: intravenous immunoglobulin

The treatment measures applied included antibiotics, immunosuppressive drugs (Corticosteroids: Dexamethasone or Prednisolone), antiviral drugs including Acyclovir or Ganciclovir; other immunosuppressive drugs (Etoposide, Rituximab, or Cyclosporin, Methotrexate), and Immunoglobulin (IVIG).

3.3.2. EBV viral load before and after treatment

Table 4: ***EBV Viral Load Before and After Antiviral Treatment***

	EBV Viral Load in Serum (cp/ml)
Before treatment	2.32×10^5 (3830 – 1.31×10^8)
After treatment	2.05×10^4 (1000 – 7.6×10^7)

Although a reduction in the median EBV viral load was observed, the extent of the decrease was insufficient to indicate effective viral control. The persistence of high viral loads in some patients following treatment suggests that the current therapeutic regimen may be inadequate or suboptimal.

3.3.3. Mortality rate over time treatment outcomes, and mortality rate over time

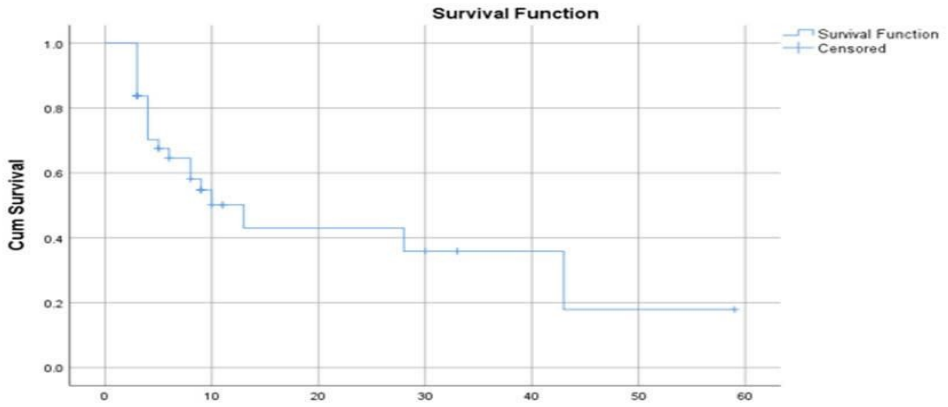

Figure 2: ***Kaplan-Meier curve showing survival probability over time***

The results demonstrate a substantial proportion of patients with unfavourable outcomes, accompanied by a progressively declining survival rate over time. Notably, the incidence of severe disease or death was high, and overall survival decreased significantly with longer follow-up durations, with the 5-year survival rate falling to below 20%.

IV. DISCUSSION

The age of onset of CAEBV in our study ranged from 1 month to 13.6 years, with a median of 41 months. According to the survey by LU Gen et al. [11], the onset of CAEBV in China ranged from 1 month to 14.6 years (mean age 5.3 ± 3.3 years). The age of onset for CAEBV in this study is similar to that found in China, but younger compared to studies from Japan and the U.S. EBV primary infection in Japan and the U.S. often occurs in adolescents and adults. In contrast, in China, primary EBV infection typically occurs at a younger age, peaking between 4-6 years [4,9]. Additionally, CAEBV is more common in Asia, including Japan, where EBV infection of T/NK cells is predominant, whereas reports from the U.S. mainly involve EBV infection of B cells [5]. Patients with T/NK cell CAEBV tend to have a younger onset age than those with B cell CAEBV (mean ages 7 years and 23 years, respectively). This difference may be related to genetic factors, HLA types, the distribution of EBV1 and EBV2 strains, and environmental factors. Further research is needed to provide a more comprehensive understanding of the epidemiological characteristics of this patient group.

The clinical and subclinical characteristics of CAEBV are diverse, affecting all organs, with notable differences between B cells and

T/NK cell CAEBV. Different immune cell functions between B, T, and NK cells result in distinct features when these cells are primarily infected with EBV, causing organ damage. Our study found that the most common symptoms were fever, hepatomegaly, splenomegaly, and lymphadenopathy. Several authors reported similar results, including Sitong Chen, LU Chen, and Ichiro Yonese, where these symptoms were present in 65% to 100% of cases. Another common symptom in our study was pulmonary involvement, observed in approximately 45% of patients, comparable to the studies by Sitong Chen and LU Chen, reporting rates of 61% and 24.5%, respectively. Reported pulmonary lesions included interstitial pneumonia (24.5%), pleural effusion (13.2%), and pulmonary hypertension (4%). Regarding cardiovascular involvement, our study recorded 9.3% of patients with cardiac issues [9,11]. Significant cardiovascular lesions included coronary artery dilation and myocarditis. Muneuchi et al. suggested that the EBV-infected CD8+ T cells may be the significant infiltrating cells in the cardiovascular lesions associated with CAEBV and that these cells contribute to the tissue necrosis and vascular damage by the enhanced release of granzyme B and perforin [12,13]. Another possible symptom is skin lesions, present in 4.7% of cases, lower than Kimura et al.[9], who reported 32.9% of 82 EBV-infected patients with mosquito bite allergies, 25.6% with rashes, and 9.8% with blisters. Less common manifestations, such as oral and gastrointestinal ulcers, were also reported. Thus, in addition to common symptoms like fever, hepatomegaly, splenomegaly, lymphadenopathy, pulmonary, cardiovascular, gastrointestinal, and skin lesions, there is a range of reported symptoms with varying frequencies. In our study, 21 patients (48.8%) exhibited HLH symptoms at the onset. Sitong Chen's [14] studied found that among 96 patients, 33 (36.3%) met the criteria for HLH. Studies have also shown that inflammatory cytokines such as interferon-gamma, IL-6, and IL-10 are elevated in CAEBV, and a cytokine storm may occur. Our research findings are consistent with Sitong Chen's results, reflecting similar symptom rates. Additionally, clinical symptoms vary depending on whether T, B, or NK cells are infected with EBV, leading to significant variability in symptom rates across studies. Histopathological studies of skin lesions have shown extensive infiltration of lymphocytes and neutrophils, with in situ hybridization tests positive for EBER, indicating abnormal viral proliferation in EBV-infected cells. Vascular lesions in CAEBV may be related to lymphocyte infiltration and endothelial damage in EBV-infected blood vessels or may occur secondarily due to inflammatory reactions caused by EBV infection [13,15].

Regarding subclinical characteristics, there were significant changes in haematological and biochemical parameters in CAEBV patients. In our research, the prevalence of leukopenia was 65.1%, anaemia was 72.1%, and thrombocytopenia was 55.8% higher than those of LU Gen et al., 39.6%, 43.4%, and 30.1%, respectively. This higher prevalence in our study can be attributed to 36.3% of our patients presenting with HLH at the time of diagnosis, leading to more pronounced haematological changes compared to their study. In our study, elevated GOT, GPT, and decreased albumin rates were 88.4%, 55.8%, and 76.7%, respectively, similar to LU Gen et al. publishing 67.9%, 69.8%, and 59.6%. Jeffrey I. Cohen et al. found that 47% of patients with hepatitis and 44% with decreased serum

albumin. LU Gen et al. [11] showed that the majority of the normal marrow cells and 100% of patients had no malignant cells. In our study, the majority had a decrease in the number of marrow cells, with 28.6% of normal marrow aspirates. This feature helps distinguish CAEBV from other diseases, manifesting as increased proliferation of EBV-infected lymphocytes infiltrating organs but not showing malignancy, so there may be decreased marrow proliferation but no malignant cells in the marrow. EBV-infected B, T, and NK cells infiltrate organs, causing organ damage, and increased inflammatory cytokines contribute to these changes. Among these factors, thrombocytopenia and decreased albumin are poor prognostic indicators.

In CAEBV, immune cell counts are altered, and immune responses are disrupted. According to LU Gen and colleagues, CD4 lymphocytes decreased <27% in 30.4% of cases, and CD8 lymphocytes increased >44% in 28.2% of cases, with CD56 (NK cells) <7% in 34.8%. Jeffrey I. Cohen's study of 19 CAEBV patients in the U.S. showed 43% with low CD19, 31% with low NK cells, 38% with low CD4, and 44% with low CD8. B-cell CAEBV had lower CD19 rates compared to T-cell CAEBV. These studies indicate changes in immune cell counts in CAEBV patients, such as decreased CD4, CD8, CD19, and CD56, with potential increases in CD8 and changes in cell function. However, no specific characteristic has been identified. Our study had a small number of patients. It did not identify the primary EBV-infected cell type infiltrating organs, limiting the description of immune changes in B, T, or NK cell CAEBV groups.

Regarding humoral immunity, 45.5% of CAEBV patients had increased IgG, and 62.5% had increased IgE in the blood. LU Chen et al. reported 39.6% of patients with elevated IgG >10 g/l and 27.1% with elevated IgE >29 U/ml. Jeffrey I. Cohen found that 42% of patients with decreased IgG. The differences may be due to the predominance of B-cell CAEBV in the U.S. – B cells produce immunoglobulins. In contrast, T and NK cell CAEBV predominates in China and Asia, where IgG levels are not reduced. NK cell CAEBV patients had higher IgE levels and increased sensitivity to mosquito bites.

Our study found that 100% of patients were VCA-IgG positive, with some patients also positive for EBNA and EA-IgG. LU Chen et al. reported 100% VCA-IgG positivity, 47% EA-IgG positivity, and 11.8% VCA-IgM positivity. These results align with high VCA-IgG positivity rates, an antibody for the viral capsid antigen that appears after the acute phase and persists for life. Along with VCA-IgG, EA-IgG is an early antigen-antibody, indicating active infection. This high VCA-IgG positivity is consistent with Okano's diagnostic criteria for CAEBV, although recent studies no longer use this antibody. Additionally, understanding the progression of these antibodies over time helps differentiate between acute, chronic, resolving, or reactivated EBV infections [10].

Therapeutic interventions included corticosteroids and antivirals used in over 90% of patients. Additional immunosuppressive agents and intravenous immunoglobulin were used in more than 60% of cases. Similar to Jeffrey I. Cohen et al. [4], treatment strategies were inconsistent. Antiviral therapy with Acyclovir and Valacyclovir was used in 63% of patients and immunoglobulin in 42%, with interferons showing no improvement. Corticosteroids were used in 79% of cases, Cyclosporin in 26%, Azathioprine in 21%, and chemotherapy in 63%, but these

treatments resulted in only transient or no responses. Some patients received EBV-specific cytotoxic T lymphocyte (EBV-specific CTLs) therapy, Rituximab, and Ganciclovir combined with Bortezomib, but these did not provide long-term effectiveness. This complexity and the lack of standardized treatment protocols highlight the challenging nature of CAEBV treatment globally and in Vietnam[16]. Our study found a median serum viral load of 2.32 x 10^5 cp/ml, which remained high after treatment. Hiroshi Kimura et al. [9] indicated that viral load did not change in patients who did not undergo hematopoietic stem cell transplantation (HSCT). Seven patients undergoing HSCT showed a significant reduction in viral load. Antiviral therapies like Acyclovir inhibit the viral DNA polymerase but not the host cell's polymerase. Thus, although Acyclovir inhibits viral replication in epithelial cells during the lytic phase, it is largely ineffective against the virus when lymphocytes divide and use the host cell's polymerase to replicate viral DNA, as in CAEBV. Immunosuppressive drugs like corticosteroids and etoposide alleviate symptoms by suppressing the inflammatory response but do not alter the disease course. Therefore, treatment must focus on suppressing inflammation and controlling abnormal cell proliferation. Japanese researchers have proposed a three-step protocol: immunosuppression to control symptoms, chemotherapy to destroy EBV-infected lymphocytes, and HSCT to restore immune function. However, these treatments' timing, cost, and efficacy require a thorough investigation in Vietnam. The mortality rate for CAEBV was high at 48.8% post-treatment, higher than the 26.2% mortality rate reported by LU Gen et al.[11] over three years, with primary causes of death being HLH, liver failure, and heart failure. Severe life-threatening complications included HLH (24.5%), interstitial pneumonia (24.5%), liver failure (15.1%), lymphoma (11.3%), neurological complications (9.4%), and disseminated intravascular coagulation (3.8%). The difference in mortality rates may be due to the varying follow-up periods and treatment methods between studies. Our study showed a 35.8±10.6% three-year survival rate. Ichiro Yonese et al. [17] studied 80 CAEBV patients in Japan and reported a 58% three-year survival rate, with 0% in the chemotherapy-only group (n=20), 65% in the chemotherapy plus HSCT group (n=47), and 82% in the HSCT-only group (n=12). Our study's higher mortality rate and lower survival rate could be due to different treatment approaches and prognoses among patients with T, B, and NK cell CAEBV. In addition to antivirals and immunosuppressives, chemotherapy and HSCT protocols are employed in Japan, China, and the U.S. HSCT, in particular, is effective, with a three-year survival rate of about 70%, depending on the country. This approach represents a promising direction for treating CAEBV patients in Vietnam.

V. CONCLUSION

The study reveals that CAEBV in pediatric patients has a severe clinical course, and prognosis is poor, leading to a high mortality rate. Therefore, further research on treatment methods is necessary to improve outcomes.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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