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Clinical Variability of Epstein–Barr Virus Infection in Children and Adults: Diagnostic Challenges

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Sultan Fariza

Adult infectious disease physician (including pediatric cases), Graduate of the Residency Program in Infectious Diseases, including Pediatric Infectious Diseases, at Kazakh National Medical University named after S.D. Asfendiyarov, Almaty, Kazakhstan.

Abstract: This article presents an analysis of the clinical variability and diagnostic challenges associated with Epstein–Barr virus (EBV) infection in pediatric and adult populations. The study is based on an interdisciplinary approach, integrating data from virology, clinical immunology, and infectious disease pathology. The analysis focuses on age-specific clinical manifestations of EBV infection, differences in immunological markers and viral load, and the complexity of laboratory data interpretation in cases of chronic active EBV infection (CAEBV). Seropidemiological data from pediatric and adult cohorts are reviewed, including studies conducted in India, China, Japan, and Taiwan. Key clinical phenotypes are systematized across age groups, with detailed descriptions of typical manifestations of mononucleosis, latent and reactivated forms. Pathogenetic associations between EBV and autoimmune conditions (notably multiple sclerosis and inflammatory bowel disease) as well as lymphoproliferative disorders are explored. Particular attention is paid to diagnostic algorithms ranging from serological panels (VCA IgM/IgG, EBNA) to molecular and cytometric methods (PCR, EBER hybridization, T/NK-cell phenotyping). The analysis reveals a high level of diagnostic uncertainty, especially in atypical pediatric cases and chronic adult forms. Proposed approaches to diagnostic standardization take into account viral persistence, immune background, and

geoepidemiological factors. The article includes three comparative tables illustrating age-related differences in clinical and laboratory features, symptom spectrum, and immunological markers of CAEBV. This work will be of value to clinicians, infectious disease specialists, immunologists, and researchers studying post-viral complications and systemic pathology associated with EBV persistence.

Keywords: Epstein–Barr virus, mononucleosis, persistence, serology, immunopathology, autoimmunity, lymphoproliferation, diagnostics, demyelination, cytometry, inflammation, chronic infection.

INTRODUCTION

In recent years, Epstein–Barr virus (EBV) infection has once again drawn the attention of clinicians and researchers due to the expanding spectrum of its clinical manifestations and the growing complexity of verifying the diagnosis in both pediatric and adult patients. Although EBV is widespread—seroprevalence reaches 90–95 percent in the adult population—a large proportion of infections are asymptomatic or present atypically, complicating timely diagnosis and clinical triage [2]. Changes in the age distribution of primary infection, noted in several developed countries, contribute to a transformation of the clinical picture, particularly among adolescents, who experience the most pronounced and prolonged manifestations of infectious mononucleosis [1].

Concurrently, the medical community's concern has increased regarding the link between persistent EBV infection and the development of chronic lymphoproliferative disorders and autoimmune conditions—among them multiple sclerosis, systemic vasculitides, and inflammatory bowel diseases. Of particular note is the phenomenon of chronic active EBV (CAEBV), which, despite its rarity, poses a serious diagnostic and therapeutic challenge, especially in pediatric practice [7].

The clinical heterogeneity and symptom overlap with other infectious, oncohematological, and autoimmune conditions demand a high index of suspicion from the physician, as well as an expanded arsenal of laboratory and instrumental methods—serological panels, PCR, and immunohistochemistry. At present, diagnostic protocols remain fragmented, making the creation of unified clinical decision-making algorithms difficult [4].

The aim of this study is to analyze the clinical variants of EBV infection across different age groups, identifying the main diagnostic challenges related to viral manifestation, persistence, and sequelae.

MATERIALS AND METHODS

The methodological foundation of this review is built on an interdisciplinary analysis of clinic-laboratory data published in peer-reviewed journals. This study focuses on a comparative examination of clinical manifestations, immunological and virological markers of EBV infection in pediatric and adult populations, and the identification of diagnostic difficulties associated with various disease forms.

The core of our analysis consists of both retrospective and prospective studies, including cohorts of children in India [4] and adult patients in China [3] and Japan [7], together with aggregated data from international observations on seropositivity dynamics and primary-infection prevalence in developed countries. Special attention was paid to differentiating primary infection, CAEBV, and EBV-associated inflammatory and oncological diseases—such as lymphoproliferative syndromes, enteropathies, and multiple sclerosis [8]. We examined three key aspects:

1. Immunological profile (including anti-capsid IgM/IgG and anti-EBNA IgG)
2. Viral load (by quantitative PCR)
3. Clinical course characteristics

Applying a narrative-analytic approach permitted stratification of data by age group and the identification of systematic gaps in diagnostic strategies. The high proportion of seronegative or atypical presentations in pediatric patients, as well as clinically manifest reactivated infection forms in adults, underscores the need to standardize diagnostic algorithms—taking into account viral load, serological profile, and clinical-epidemiological factors.

Results and Discussion

Diagnostic algorithms used across various geographic and age cohorts were examined, with particular emphasis on the applicability of serological panels in early diagnosis and their sensitivity at different stages of the disease [2].

The comparison of these parameters is summarised in Table 1, which presents data on the prevalence of key laboratory markers and clinical signs in pediatric versus adult populations. The findings demonstrate a clear age-related shift in primary manifestation: adolescents and young adults more often present with infectious mononucleosis, whereas older individuals more commonly harbor latent forms with a high risk of reactivation.

Table 1 – Comparative characteristics of laboratory markers and clinical features of EBV infection in pediatric and adult patients (Compiled by the author based on sources: [1], [3], [4], [5])

Parameter	Pediatric Population	Adult Population
Seropositivity for VCA IgG	75–80 %	> 95 %
Frequency of VCA IgM positivity (acute phase)	8.6 %	12–15 %
Absence of EBV-specific antibodies	23.4 %	< 2 %
Presence of EBNA IgG	Increases around age 4–5	Persistently high
Plasma EBV DNA levels (copies/mL)	Not routinely detected in acute pediatric cases	> 10^4 copies/mL in CAEBV
Frequency and severity of CAEBV	Rare, mostly in adolescents	More severe and progressive
Association with chronic diseases (e.g., IBD)	Not documented	Strong correlation with IBD, autoimmunity
Diagnostic complexity	Seronegative window; non-specific symptoms	Overlapping syndromes, reactivation, malignancies

As evident from the comparative table, the clinical and serological manifestations of EBV infection differ substantially between children and adults, which dictates the distinct nature of disease progression and diagnosis in these age groups. EBV exhibits broad clinical variability, particularly when comparing pediatric and adult populations. In most cases, primary infection in childhood proceeds subclinically, whereas in adolescence and adulthood it more frequently manifests as infectious mononucleosis (IM) [2].

In early childhood, EBV infection often does not cause pronounced symptoms. According to seroepidemiological studies, infection typically occurs between ages 1–3 years and is either asymptomatic or

accompanied by nonspecific signs such as low-grade fever and lymphadenopathy. However, atypical and severe forms can arise, including CAEBV, which in children and adolescents tends to run a more protracted but less aggressive course compared to adults [7].

Among adolescents and adults, primary infection more often presents with the classic clinical picture of IM: fever, pharyngitis, generalized lymphadenopathy, hepatosplenomegaly, and pronounced asthenic syndrome. Unlike in the pediatric population, adult patients face a higher risk of complications, including hematological manifestations (thrombocytopenia, hemolytic anemia), neurological involvement (meningitis, encephalitis), and hepatic features (hepatitis) [6].

CAEBV represents a rare yet clinically significant form of EBV infection seen in both children and adults, particularly prevalent in Asian countries. CAEBV is characterized by persistent IM-like symptoms, hypercytokinemia, T/NK-cell involvement, and a high risk of progression to lymphoproliferative disorders, including lymphoma and hemophagocytic lymphohistiocytosis (HLH). In adults, the disease course is more rapid, more aggressive, and often necessitates early immunosuppressive therapy or hematopoietic stem-cell transplantation [7].

Diagnostic difficulty arises from multisystem involvement, the absence of pathognomonic signs, and cross-reactive serological results—especially in the setting of secondary immunodeficiencies and concurrent infections [3]. Table 2 below systematises the main clinical presentations of EBV infection by age group.

Table 2 – Spectrum of Clinical Manifestations of EBV Infection by Age Group (Compiled by the author based on [2], [4], [6], [7])

Age Group	Main Clinical Manifestations	Frequency of CAEBV	Course Characteristics
Children (0–5 years)	Asymptomatic, low-grade fever, lymphadenopathy	Sporadic	Often undiagnosed; rare severe forms
Adolescents (6–18)	Classic IM: fever, pharyngitis, hepatosplenomegaly	Possible; tends to chronicity	Higher risk of complications compared to younger children
Adults (>18 years)	Pronounced IM: hepatitis, lymphocytosis, fatigue	Rare, but with aggressive course	High risk of lymphomas, HLH, and central-nervous-system involvement

Clinical polymorphism in EBV infection is determined both by the patient's age at the time of infection and by their immune response status. Given the risk of underrecognising severe forms in young children and progressive forms in adults, timely differential diagnosis and ongoing monitoring of viral activity—particularly in high-risk groups—remain essential.

Diagnosing EBV infection, especially in chronic or atypical cases, poses a substantial clinic-laboratory challenge. These difficulties stem from the wide spectrum of clinical phenotypes and the intricacies of the host immune response to EBV—including viral persistence, latency, and serological paradoxes [3].

Immunological diagnosis relies primarily on serological markers—namely, antibodies against the viral capsid antigen (VCA IgM and VCA IgG), the nuclear antigen

(EBNA IgG), and early antigens (EA). However, EBV's latent behavior frequently leads to misleading interpretations: patients with active viral replication may exhibit a serological profile of VCA IgM–, EBNA+, and VCA IgG+, which typically indicates latency but can mask ongoing infection [3], [4]. Interpreting the immune profile is especially challenging in cases of chronic active EBV (CAEBV). In these patients, persistent or intermittent viral activity—accompanied by high levels of EBV DNA in peripheral blood mononuclear cells—can coexist with stable or even falsely negative serological results. Diagnosing CAEBV therefore requires integrating molecular techniques—quantitative PCR and in situ hybridisation for EBV-encoded RNA (EBER)—as well as immunohistochemical and flow-cytometric analyses to detect infected T- or NK-cells [7]. Additionally, cross-reactivity between EBV antigens and those of other herpesviruses or self-antigens further complicates serological interpretation. Such cross-reactivity is particularly pronounced in patients with immune dysregulation or underlying autoimmune conditions. Table 3 summarises the key immunological and laboratory markers used to diagnose EBV infection and CAEBV, detailing their diagnostic value and common interpretive pitfalls.

Table 3 – Key Immunological and Laboratory Diagnostic Markers in EBV and CAEBV (Compiled by the author based on sources: [3], [4], [6], [7])

Marker / Method	Diagnostic Relevance	Interpretation Challenges
VCA IgM / VCA IgG	Differentiates primary infection from past exposure	False negatives may occur in early acute or latent cases
EBNA IgG	Indicates past infection	May be absent in immunodeficient patients
EBV DNA (PCR, blood mononuclear cells)	Monitors viral load; confirms CAEBV	Threshold values vary and lack standardisation
EBER (in situ hybridisation)	Detects EBV-infected cells in tissue	Requires invasive tissue samples; low sensitivity in peripheral blood
Flow cytometry (T/NK-cell subsets)	Phenotyping for CAEBV	Limited availability; typically only in specialised centres
Cross-reactive antibodies (ANA, RF, etc.)	May reflect antibody responses to EBV or mimic autoimmune disease	Can lead to misdiagnosis, especially in patients with background autoimmunity or immune dysregulation

Chronic persistence of EBV after primary infection is not merely a clinical curiosity but a potential pathogenic mechanism for a broad spectrum of autoimmune and neoplastic conditions. Although in the majority of cases the virus remains latent and asymptomatic, recent data demonstrate EBV's active role in initiating and sustaining chronic inflammatory processes and malignant transformations [8].

One of the most extensively studied associations

between EBV and autoimmunity is multiple sclerosis (MS). Immunological and molecular investigations reveal that EBV persistence within B-cells can trigger cross-reactive T-lymphocytes directed against myelin proteins, leading to demyelination in the central nervous system [6]. Moreover, the detection of EBV-infected cells within meningeal infiltrates in MS patients strengthens the hypothesis of viral involvement in neuroinflammation.

Beyond neurological disorders, mounting evidence links EBV to inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis. A large Taiwanese cohort study demonstrated that EBV infection was associated with a more than twofold increased risk of developing IBD (hazard ratio > 2.0), with the highest risk observed in individuals exhibiting elevated viral loads or latent persistence [8]. These findings suggest an immune-mediated mechanism by which chronic activation of EBV-infected lymphocytes damages the intestinal mucosa.

The worst outcomes occur in CAEBV. This form is characterised by sustained viral replication in T- and NK-cells, pronounced hypercytokinemia, and a high risk of transformation into malignant lymphoid tumours—specifically, T/NK-cell lymphomas and aggressive leukaemias. Most CAEBV patients develop hepatic, splenic, bone-marrow, and central-nervous-system involvement; prognosis hinges on the timely administration of haematopoietic stem-cell transplantation.

Thus, EBV cannot be dismissed as a merely benign or "routine" pathogen. Its ability to persist and to mediate immune-driven tissue damage positions it as a central player in the pathogenesis of both autoimmune and malignant diseases. In light of the growing body of evidence linking EBV to systemic dysfunction, it is crucial to advance early molecular diagnostics and to develop immunotherapeutic strategies that specifically suppress EBV-positive cell populations.

CONCLUSION

This study has elucidated the principal clinical and immunological features of EBV infection across different age groups and highlighted the key challenges encountered during diagnosis, laboratory-marker interpretation, and assessment of the infection's long-term consequences.

Our analysis demonstrated pronounced age-related differences in clinical presentation: in children, EBV infection often runs asymptomatically or in a smouldering form, whereas in adolescents and adults, the infection more commonly manifests as classic infectious mononucleosis. Of particular concern is chronic active EBV (CAEBV), which follows a severe, progressive course with a high risk of lymphoproliferative complications and necessitates multi-stage immunocytotoxic therapy.

A central problem remains diagnostic uncertainty. The virus's latent state, cross-reactive immune responses, and atypical antibody profiles (IgM−/IgG+) impede early detection—especially where molecular diagnostics are not readily available. This can lead to underdiagnosis of CAEBV, particularly in paediatric practice, and to delayed initiation of therapy, thereby worsening the prognosis. Our evaluation of long-term sequelae identified links between EBV and both autoimmune and oncological conditions. Specifically, we examined viral contributions to the pathogenesis of multiple sclerosis, inflammatory bowel disease, and lymphoma. These findings underscore the necessity for long-term follow-up of patients who have experienced EBV infection—especially in cases of immune dysfunction or high viral load.

In summary, EBV infection is not merely an episodic viral illness but a significant risk factor for systemic disorders. Its diverse clinical phenotypes, diagnostic complexity, and serious long-term implications demand a comprehensive approach—incorporating seroepidemiological surveillance, early molecular confirmation, and the development of individualized treatment and prevention strategies. Future research in this field should focus on advancing anti-EBV vaccine development, deepening our understanding of the immune pathogenic mechanisms underlying viral persistence, and integrating highly sensitive diagnostic algorithms into clinical practice.

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