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Research Advances in Infectious Mononucleosis Caused by Epstein-Barr Virus

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Abstract

Infectious mononucleosis (IM), primarily caused by the Epstein-Barr virus (EBV), manifests as the classic triad of fever, pharyngitis, and cervical lymphadenopathy. Severe cases may involve organ damage, most commonly affecting the liver. Diagnosis relies on a combination of clinical presentation and laboratory parameters, with commonly used indicators including EBV-specific antibodies, EBV-DNA load, and the ratio of atypical lymphocytes. Treatment primarily involves symptomatic supportive care, with a cautious approach to the routine use of antiviral medications. In recent years, significant research in traditional Chinese medicine has been conducted in China, showing promising advancements. This article provides a comprehensive review of EBV-induced infectious mononucleosis, offering insights for clinical diagnosis and treatment.

Keywords

Epstein-Barr Virus, Infectious Mononucleosis, Children

1. Introduction

Infectious mononucleosis, commonly referred to as "mono," is one of the most prevalent diseases in childhood. Relevant data indicates that the majority of IM cases are caused by infection with the Epstein-Barr virus. IM is characterized as a proliferative disorder of the mononuclear-macrophage system in the body. The primary clinical manifestations include the classic triad of fever, pharyngitis, and lymphadenopathy, along with additional clinical features such as rash, and hepatosplenomegaly [1]. Due to the nonspecific initial symptoms and variable onset presentations of IM, coupled with the potential for organ damage, clinical misdiagnosis and underdiagnosis are common. This article systematically describes the research progress in the epidemiology, transmission pathways, pa-

thogenic mechanisms, clinical features, laboratory examinations, diagnosis, and treatment of infectious mononucleosis caused by the EBV. The aim is to provide insights for clinical diagnosis and treatment, considering the lack of specificity in the clinical presentation of IM at the onset.

2. Epidemiology

Existing research has firmly established the Epstein-Barr virus as the primary pathogen responsible for infectious mononucleosis. Following EBV invasion into the human body, a latent period of 1 - 2 months ensues, culminating in the development of infectious mononucleosis. The relationship between IM incidence and seasons as well as age remains a subject of debate.

2.1. Correlation between Season and Incidence of IM

IM caused by EBV can occur throughout the year, but the correlation between seasons and IM incidence remains inconclusive. A retrospective analysis conducted by Yuan L. P. and colleagues on 193 hospitalized IM patients at the First Affiliated Hospital of Anhui Medical University showed that a relatively higher incidence of IM in the summer and late autumn to early winter [2]. In contrast, Gao Y. [3] conducted an epidemiological retrospective study on 73 pamphlet patients admitted to the First Affiliated Hospital of Kunming Medical University, finding that spring and summer are the peak seasons for incidence. The author postulates that the disparity in research outcomes may be attributed to variations in study duration and geographical locations. Anhui Province is located further north compared to Kunming City, experiencing significant temperature changes from late autumn to early winter, which leads to a higher incidence rate of respiratory infections among children.

2.2. Association between Age and Incidence of IM

EBV-induced IM can manifest in all age groups. A 2022 nationwide retrospective epidemiological study on hospitalized children with IM in China showed that the most hospitalizations occurred among children aged 4 - 6 years, accounting for 0.85% of all hospitalizations, followed by ages 1 - 3 years, 7 - 12 years, 13 - 18 years, and 0 - 1 year [4]. In contrast, developed countries demonstrate a first incidence peak in adolescence. An epidemiological study based on hospitalized patients in the United Kingdom found that the peak of hospitalizations for IM patients was at 15 - 19 years, significantly higher than other age groups [5]. The author posits that the higher age of initial incidence in developed countries may be associated with socio-economic factors and healthcare. Furthermore, studies by foreign scholars suggest that older children and young adults who are not previously infected with EBV are more susceptible to developing infectious mononucleosis upon primary infection with the virus [6].

3. Routes of Transmission

Epstein-Barr virus exhibits a widespread susceptibility in the human population,

with humans being the sole host for EBV. Following invasion into the human body, EBV can manifest as either a proliferative or latent infection, making potential sources of transmission include patients, carriers with latent infections, and asymptomatic carriers. As EBV initially targets the epithelial cells of the oropharynx and resting B lymphocytes, and subsequently attacks the epithelial cells of the salivary glands, a significant amount of EBV is present in the saliva, and shedding can persist for several months to over a year. Therefore, respiratory droplets and oral-oral transmission are considered the primary modes of transmission [7]. A prospective study on infectious mononucleosis conducted by Grimm and his colleagues found that deep kissing is the only risk factor for the disease, leading to the nickname "the kissing disease" for IM [8]. Pre-adolescent children may contract EB virus through shared eating utensils or from virus-carrying parents via pre-chewed food transmission [9] [10]. While there are reports suggesting other transmission routes such as blood transfusion, organ transplantation, sexual contact, and vertical transmission from mother to infant, these modes are not commonly observed in children [11].

4. Pathogenic Mechanisms

The exact pathogenic mechanisms of infectious mononucleosis remain inconclusive. Most scholars generally agree that IM caused by EBV results from immune imbalance induced by EBV invasion into the human body. The pathogenesis of EBV infection primarily includes latent infection and lytic replication. EBV mainly targets oropharyngeal epithelial cells and B lymphocytes. EBV first infects the epithelial cells through membrane fusion and endocytosis, then undergoes lytic replication within these cells. Subsequently, progeny viral particles infect B lymphocytes by binding to the B cell surface receptors CD21 and CD35 through the viral surface protein gp350/220, and also by binding of viral surface GP42 protein to Major Histocompatibility Complex (MHC) II molecules on B cells, entering through membrane fusion. Once inside the B cell, EBV does not immediately proceed with extensive replication but instead enters a latent phase, integrating its genome into the host cell's DNA. During this period, EBV expresses only a limited set of viral proteins, such as Latent Membrane Proteins (LMPs), EBV Nuclear Antigens (EBNAs), and a small amount of small non-coding RNAs. These proteins help maintain the latent state while also promoting the survival and proliferation of infected B cells post-infection [12] [13].

When various factors lead to immunosuppression, EBV infection shifts from latency to the lytic phase. During this period, EBV replicates extensively within oropharyngeal B lymphocytes and epithelial cells, lytically releasing viral particles in the oropharynx while simultaneously activating the body's non-specific and specific immune responses. The non-specific immune response involves macrophages and natural killer cells (NK cells) recognizing and eliminating virus-infected cells, accompanied by the release of cytokines and chemokines, such as interferons and tumor necrosis factors, to enhance immune reactions and ac-

tivate specific immunity. The resulting inflammatory response, manifesting as fever, pharyngitis, etc., helps to limit pathogen spread and repair tissue damage caused by viral infection [14].

The body's specific immunity, especially cellular immunity, plays a crucial role in the infection of EBV. In the early stages of the disease, EBV-infected B cells proliferate massively, inducing the body to generate a large number of cytotoxic T lymphocytes (CTLs), namely CD8+ T cells, under the influence of cellular immunity. CTLs are activated by recognizing viral antigen peptides presented by MHC I molecules. After proliferating extensively, they target and attack EBV-infected cells by releasing perforin and granzymes. Some activated CD8+ T cells differentiate into memory T cells, which continue to monitor the EBV infection status in the body after infection control, ready to respond rapidly to reactivation of the latent virus. Meanwhile, CD4+ T cell receptors (TCR) recognize EBV-specific antigens presented by MHC II molecules, and the cell surface CD28 binds to ligands such as CD80 and CD86 on the antigen-presenting cell surface, activating and proliferating CD4+ T cells. They differentiate into various subtypes such as Th1, Th2, and Treg, releasing various cytokines to assist in the activation and proliferation of CD8+ T cells and B cells, such as interferon-gamma and various interleukins (IL-2, IL-4, IL-10, etc.). Some activated CD4+ T cells differentiate into memory T cells, achieving long-term immunity effects [15]. Researches have found that during the acute phase of IM, there is a predominant increase in CD3+, CD8+ lymphocytes, accompanied by a decrease in the proportion of CD4+, CD16+, CD56+, and CD19+ cells. It is believed that the immune response to EBV primarily involves both innate and adaptive immunity, with CD3+, CD8+ playing a significant role. Additionally, during the recovery phase, there is a decrease in the proportion of CD3+, CD8+, suggesting that the expansion of CD8+ cells may be the main cause of the clinical manifestations in the acute phase of IM [16] [17].

Furthermore, genetic factors may also contribute to the development of IM. Foreign studies have found that the incidence of IM in monozygotic twins is twice that of dizygotic twins, and the incidence decreases in first-degree, second-degree, and third-degree relatives in that order. Specific research in China is lacking to demonstrate the correlation between genetics and IM, warranting further investigation for confirmation [18] [19].

5. Clinical Features

Patients with IM commonly present with the "triad" of fever, pharyngitis, and cervical lymphadenopathy during the acute phase. This characteristic symptom triad typically raises the physician's suspicion of IM, prompting further examination and laboratory testing, and it shows no significant differences across various age groups and may also include nasal congestion, rash, periorbital edema, hepatosplenomegaly, and other symptoms. While these symptoms do not occur in all patients, their presence can aid in supporting the diagnosis of IM when they do appear. Fever is the most prevalent presentation, often reaching peaks

around 39˚C and lasting for 1 - 2 weeks, motivating most patients to seek medical attention. Pharyngotonsillitis, encompassing both pharyngitis and tonsillitis, follows as the second most common symptom. Some patients present with sore throat, enlarged tonsils with purulent exudate, and fever as initial symptoms, which are clinically likely to be misdiagnosed as acute purulent tonsillitis. It is important to complete relevant auxiliary examinations, such as Epstein-Barr virus-specific antibody tests and peripheral blood atypical lymphocyte detection, to help further differentiate and diagnose [20]. Cervical lymphadenopathy typically manifests as painless enlargement on both sides. IM-associated rashes exhibit diverse morphologies, lack desquamation during eruptions, and resolve without pigmentation after IM improvement. Infants and toddlers show a higher incidence of rashes compared to preschool and school-age children, possibly linked to a higher susceptibility to hypersensitivity reactions in younger age groups [21]. Additionally, the correlation between antibiotic use and the risk of rash in IM patients remains inconclusive. Some studies indicate a notable increase in rash incidence when antimicrobial drugs are administered early in the disease, with ampicillin demonstrating an 80% - 100% rash occurrence rate [22] [23]. The use of amoxicillin is also frequently reported to be associated with rashes. However, a Meta-analysis conducted by Zhang J. X. on the correlation between antibiotic use and rash risk in IM patients since 1976 showed no apparent connection [24]. The risk of rash occurrence varied between ampicillin and amoxicillin use, suggesting that amoxicillin might not be associated with an increased risk of rash. In some cases, periorbital edema may be the initial symptom leading to medical consultation, even surpassing rashes and hepatosplenomegaly. Cervical lymphadenopathy causing obstruction of lacrimal lymphatic reflux may be the primary cause of eyelid edema and holds significant value in the diagnosis of atypical IM cases. When children present with eyelid swelling, after excluding ocular diseases, renal disorders, immune system diseases, and other conditions, the possibility of Epstein-Barr virus infection should be considered [25].

Due to the wide-ranging impact of the EBV on multiple systems, patients with IM may experience various systemic complications, affecting the respiratory, circulatory, hematologic, digestive, and nervous systems, among others. Research conducted both domestically and internationally has identified respiratory complications as the most common. These may manifest as bronchitis, interstitial pneumonia, pleural effusion, and, in some cases, respiratory distress or difficulty breathing during the acute infection period or due to factors such as tonsillar or lymph node enlargement. Improper management of these symptoms can pose a life-threatening risk [26]. The primary manifestation of complications related to the digestive system is liver damage. Over 70% of IM patients exhibit abnormal liver function during the acute phase, characterized mainly by elevated transaminase levels. Liver enzyme levels can be normalized through hepatoprotective medication, but a minority of patients may experience jaundice, and an extremely small number may develop acute liver failure. Additionally, spleno-

megaly is a common complication, occurring in over 50% of patients. Infiltration of the spleen parenchyma by a large number of lymphocytes and monocytes leads to increased spleen volume and fragility. External force or increased internal organ pressure can easily result in splenic rupture and bleeding [27] [28]. Complications involving the hematologic system may manifest as neutropenia, thrombocytopenia, anemia, and other abnormalities. Circulatory system complications may include myocardial damage, abnormal electrocardiograms, acute pericarditis, among others. A small number of patients may experience neurological complications, such as viral encephalitis or Guillain-Barré syndrome [26].

6. Laboratory Examinations

6.1. Complete Blood Count and Atypical Lymphocyte Testing

In patients with infectious mononucleosis, white blood cell and lymphocyte counts are typically elevated compared to normal values. The proportion of atypical lymphocytes can exceed 10%. However, research indicates that in almost half of preschool children, the proportion of atypical lymphocytes is less than 10% [29]. Additionally, peripheral blood can be assessed for the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR). NLR and MLR, as inflammatory markers, to some extent, reflect the immune status of the body and are correlated with various diseases. Studies have shown that in children with IM, NLR and MLR are inversely correlated with liver damage, making them potential laboratory indicators for assessing the severity of the condition [30] [31].

6.2. Laboratory Diagnostic Methods for Epstein-Barr Virus (EBV) Infection

Early detection of EBV infection is crucial in aiding the diagnosis of infectious mononucleosis. Laboratory methods for EBV detection include heterophilic agglutination tests, Epstein-Barr encoded small RNAs (EBERs) in situ hybridization assay, EBV-specific antibody assays, EBV-DNA load measurement, and EBV virus culture. Heterophilic agglutination tests, considered the most commonly used serological assay, offer advantages such as distinguishing primary from recurrent infections, cost-effectiveness, and simplicity. However, due to lower sensitivity and specificity in children, its clinical use has diminished. EBERs in situ hybridization assays, regarded as the gold standard for clinical EBV diagnosis, are often performed on pathological tissues. While operationally complex, they are primarily employed in diagnosing EBV-related tumors. Different stages of IM are associated with different EBV-specific antibodies. For immunocompetent children, testing for antibodies including viral capsid antigen (VCA)-IgM, VCA-IgG, and Epstein-Barr nuclear antigen (EBNA)-IgG can differentiate recent infection from past infection. In the early stage of the disease, a significant increase in VCA-IgM is observed, serving as a hallmark of recent EBV infection, with specificity and high sensitivity, lasting for 4 - 8 weeks, and

being a major basis for clinical diagnosis. VCA-IgG antibodies are primarily low-affinity antibodies during the acute phase, transitioning to high-affinity antibodies during the recovery period. EBNA-IgG antibodies typically appear in the late stages of infection and may persist for life, a positive result indicates a past infection. It is important to note that although VCA-IgM antibodies are specific to EBV, they can also be positive in cytomegalovirus infection. Epstein-Barr virus DNA load serves as a direct indicator of viral replication within the host [32]. While EBV DNA load testing has not yet been established as a mandatory auxiliary examination for infectious mononucleosis in clinical practice, Research from the Northern Hospital of Xi'an City indicates that the combined assessment of EBV-VCA-IgM and real-time Polymerase Chain Reaction (PCR) for EBV-DNA load significantly improves sensitivity and accuracy in diagnosing IM compared to individual tests [33]. EBV virus culture is not commonly used in clinical diagnosis of IM due to its lengthy incubation period (2 weeks to 2 months), time-consuming nature, high cost, and complex technical requirements [34].

6.3. Others

Certain cases of infectious mononucleosis may present with complications such as hepatic and cardiac involvement, as evidenced by elevated levels of transaminases, creatine kinase (CK), and/or CK-MB in laboratory examinations. Moreover, findings by Ting S. *et al.* [35] suggest that adenosine deaminase (ADA) exhibits high diagnostic accuracy in predicting IM and anticipating elevated alanine transaminase (ALT). ADA not only aids clinicians in early IM diagnosis but also serves as an indirect indicator of disease severity.

7. Diagnosis

In accordance with the latest 2021 Expert Consensus on the Diagnosis and Treatment Principles of EBV-Related Diseases in Children in China [36], the diagnostic criteria for IM involve three key components: clinical manifestations, laboratory evidence, and nonspecific laboratory indicators. Clinical diagnosis requires meeting any three clinical manifestations and any one nonspecific laboratory indicator, while confirmed cases necessitate meeting any three clinical manifestations and any one laboratory evidence. Typical clinical manifestations: 1) fever, 2) pharyngitis, 3) cervical lymphadenopathy, 4) hepatomegaly, 5) splenomegaly, 6) periorbital edema. Specific laboratory evidence: 1) positivity for a VCA-IgM and VCA-IgG antibodies with negativity for EBNA-IgG, 2) positivity for VCA-IgG antibodies with low-affinity antibodies. Nonspecific laboratory indicators: 1) peripheral blood atypical lymphocyte proportion ≥10%, 2) for children aged six and above, peripheral blood lymphocyte proportion >50% or absolute lymphocyte count $>5.0 \times 10^9$/L. Although the necessity of quantifying EBV-DNA is not mentioned in the expert consensus, studies have found that the combined diagnostic specificity (96.63%) of EBV-VCA-IgM and EBV load is

higher than that of either test alone, contributing to improved diagnostic efficacy [37].

8. Treatments

Infectious Mononucleosis IM is a benign, self-limiting disease with a generally favorable prognosis, and its management primarily involves symptomatic and supportive care, including rest, antipyretics, and hepatoprotective measures. The use of antiviral medications remains inconclusive, as they may reduce viral replication and pharyngeal shedding duration but show no significant impact on treatment efficacy or prognosis. Studies have indicated that the application or non-application of antiviral drugs does not result in a significant difference in IM treatment outcomes [38]. A systematic review by De Paor M. *et al.*, which included 7 randomized controlled trials, indicated that clinical recovery time and duration of lymph node swelling were significantly reduced in patients treated with antiviral therapy using acyclovir, valacyclovir, and famciclovir compared to the control group, with statistical significance. However, the use of antiviral drugs did not reduce the incidence of complications [39]. Commonly used antiviral drugs in China include acyclovir, famciclovir, valacyclovir, interferon-α1b, and acadesine, but their efficacy requires further investigation [40]. A multicenter retrospective study conducted in China analyzed the clinical characteristics and effectiveness of antiviral therapy in 499 hospitalized pediatric patients. About half of the patients received ganciclovir treatment, while approximately one-quarter received acyclovir treatment. Comparing patients who received antiviral treatment with those who did not, it was found that the treated patients presented more severe symptoms, such as longer fever duration [41]. Additionally, a systematic analysis of the effectiveness and safety of α-interferon (IFN-α) treatment in infectious mononucleosis showed that the use of IFN-α could reduce the occurrence rate of neutropenia, and nebulized administration significantly shortened the time for temperature reduction. However, the other efficacies and safety of IFN-α have not yet been confirmed [42]. Short-term corticosteroid therapy may be considered for patients with airway obstruction or autoimmune complications [43]. Additionally, due to the risk of splenic rupture, physical activity should be avoided or minimized, and bed rest is recommended for at least 2 - 3 months after symptom relief [10] [44].

In recent years, there has been a growing exploration of the use of traditional Chinese medicine (TCM) formulations as adjunctive therapy for IM in China, showing promising progress. The most commonly employed categories are heat-clearing and detoxifying agents and blood-activating and stasis-removing agents [45]. For instance, studies by Xie H. D. [46] found that the Qingyan Lige Tang formulation is beneficial for the prognosis of IM. The total effective rate of treatment exceeds 90%. After treatment, there is a decrease in peripheral blood white cell count, atypical lymphocyte percentage, aspartate aminotransferase, EB virus antigen, and viral load compared to before treatment. The liver, spleen,

and cervical lymph nodes gradually shrink, indicating effective treatment, and no serious complications occurred in all cases. Xu X. M. [47] reported that Patients treated with the combination of Heat Toxin-Calming Formula and acadesine showed a higher total effective rate (93.3%) compared to those treated with acadesine alone (80%). After combined treatment, the level of CD4+ T cells decreased while the level of CD8+ T cells increased compared to before treatment, favoring the improvement of immune balance. Moreover, the incidence rate of adverse reactions was not significantly different compared to monotherapy. And Sun X. X. [48] randomly divided 70 children with IM into an observation group of 35 and a control group of 35. The observation group was treated with Si Miao Qing Wen Bai Du Yin combined with ganciclovir, while the control group was treated with ganciclovir alone. The study results showed that the total effective rate of the observation group (94%) was higher than that of the control group (30%). The time taken for improvement of fever, pharyngitis, cervical lymph nodes, and hepatosplenomegaly in the observation group was shorter than that in the control group. The levels of CD4+, CD4+/CD8+, ALT, and AST were higher in the observation group than in the control group, while the levels of CD8+, atypical lymphocyte ratio, and EBV-DNA load were lower than those in the control group. Therefore, Si Miao Qing Wen Bai Du Yin as an adjunctive treatment can enhance immune function, improve traditional Chinese medicine syndromes, and shorten the course of the disease. This is consistent with the findings of Yan Y. B. and others [49]. However, the changes in immune mechanisms induced by combined traditional Chinese medicine therapy remain unclear and require further investigation.

IM is prevalent and highly susceptible among Chinese children, making prevention and control of EBV infection crucial. EBV invasion into cells involves various membrane glycoproteins, including gp350, gH/gL, gB, gp70, gp42, among others. The research on vaccines targeting the membrane glycoprotein gp350 of EBV has made initial progress. Studies indicate that combination immunization with gH/gL, gB, and/or gp70 significantly increases EBV neutralization activity compared to immunization with individual proteins. Therefore, incorporating gH/gL and gB into gp350 vaccine formulations is being explored as a feasible approach for a new prophylactic EBV vaccine. Additionally, research on therapeutic EBV vaccines is underway, although progress is slow. Hence, vaccine development remains a critical area of focus in the coming years [50].

9. Conclusion

Infectious mononucleosis caused by the EBV is a common clinical condition, and its incidence has been on the rise in recent years. In China, the onset of IM is predominantly concentrated in the preschool and school-age periods. During the acute phase of IM, typical manifestations include fever, pharyngitis, and lymphadenopathy. Some patients may also experience hepatosplenomegaly, rash, and periorbital edema. Current research suggests that the clinical manife-

stations in IM patients are largely a result of immune reactions triggered by EBV infection. Symptoms in immunocompetent patients typically resolve spontaneously within 1 - 2 weeks, without the need for antiviral or other specific treatments. Given the potential for EBV to establish long-term latent infections and its association with the development of cancers and various autoimmune diseases, early prevention and treatment of EBV are crucial. In recent years, there has been initial progress in the development of EBV vaccines, contributing to early prevention of EBV infection and targeted treatment of EBV-related diseases. However, the pathogenesis of EBV-related IM and the development of vaccines remain unclear, necessitating further research. Additionally, analyses of IM are predominantly retrospective, with clinical uncertainties and numerous confounding factors, highlighting the need for more comprehensive prospective studies to enhance our understanding of the condition.

Author Contribution

Yuying Wang conducted literature search, data extraction and manuscript drafting. Peng Chen conceived the study and supervised the entire process of the study. Both authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

IM	Infectious mononucleosis
EBV	Epstein-Barr virus
MHC	Major histocompatibility complex
LMPs	Latent membrane proteins
EBNAs	EBV nuclear antigens
NK cells	Natural killer cells
CTLs	Cytotoxic T lymphocytes
TCR	T cell receptors
NLR	Neutrophils to lymphocytes
MLR	Monocytes to lymphocytes
EBERs	Epstein-Barr encoded small RNAs
VCA	Viral capsid antigen
PCR	Polymerase chain reaction
CK	Creatine kinase
ADA	Adenosine deaminase
ALT	Alanine aminotransferase
IFN-α	*α*-interferon
TCM	Traditional Chinese medicine