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Original Article

Impact of Epstein-Barr virus infection on the development and prognosis of allergic purpura

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Abstract

Introduction: This study aimed to examine the impact of Epstein-Barr virus (EBV) infection on the occurrence and prognosis of Henoch-Schönlein purpura (HSP).

Methodology: A total of 120 children diagnosed with HSP were selected as the experimental group, and 100 healthy children who underwent physical examinations were the control group. We compared renal function markers and quantified 24-hour urine protein in HSP children with different EBV infection statuses, and analyzed the association between EBV infection and Henoch-Schönlein purpura nephritis (HSPN).

Results: The detection rate of EBV-DNA load in the experimental group (30.83%) was significantly higher than that in the control group (10.00%) ($p < 0.05$). Among children with HSP, the detection rate of EBV-DNA load was significantly higher in those with abdominal involvement compared to those with joint or mixed types ($p < 0.05$). Serum levels of serum creatinine, blood urea nitrogen, and urine protein quantification were significantly higher in the EBV-positive group than in the EBV-negative group ($p < 0.05$). The detection rate of EBV-DNA load was significantly higher in the HSPN group compared to the non-HSPN group ($p < 0.05$). The detection rate of EBV-DNA load was significantly higher in the recurrence group than in the non-recurrence group ($p < 0.05$), and it was also higher in the relapse group compared to the non-relapse group ($p < 0.05$).

Conclusions: EBV infection is associated with the development of HSP; and gastrointestinal, joint, and renal damage. It is also an early warning sign for disease recurrence, which highlights its clinical significance.

Key words: EBV; allergic; HSP; HSPN; characteristics; prognosis.

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Introduction

Henoch-Schönlein purpura (HSP) is a common autoimmune disorder in childhood that is characterized by purplish-red bruised spots or plaques on the skin. On average, HSP is estimated to affect approximately 10 to 20 per 100,000 children annually [1]. It is more common in children between the ages of 2 and 11 years, with a slight male predominance.

Joint pain and swelling are common in HSP, often affecting the knees and ankles. Joint symptoms can be transient or recurrent; and in some cases, they may persist for several months. Rarely, individuals may develop more severe joint complications, such as arthritis or joint deformities. HSP can also involve the gastrointestinal tract, leading to abdominal pain, nausea, vomiting, and occasionally, gastrointestinal bleeding [2,3]. The severity of gastrointestinal symptoms can vary, ranging from mild discomfort to more serious complications, such as intussusception or bowel perforation. Some individuals with HSP may experience systemic symptoms, including fever, malaise, and fatigue [4]. These symptoms are typically self-limiting and resolve as the disease progresses.

The kidneys can be affected in a significant proportion of HSP cases, resulting in a condition called Henoch-Schönlein purpura nephritis (HSPN). HSPN can manifest as hematuria (blood in the urine), proteinuria (protein in the urine), and, in rare cases, kidney impairment or failure. Long-term follow-up is crucial to monitor the renal function and detect any potential complications. Approximately 30% to 50% of HSP children have HSPN, which damages the kidney and can be life-threatening in severe cases [2,5]. HSPN is believed to be associated with platelet disorders,

coagulation abnormalities, and infectious agents [3–5].

Recently, there has been interest in the role of Epstein-Barr virus (EBV) infection in HSP. EBV is a member of the herpesvirus family and is one of the most common viruses in humans. Some clinical reports have suggested a link between EBV infection and HSP [6]. Some studies have reported a higher detection rate of EBV infection in individuals with HSP, compared to healthy controls or individuals with other diseases [7,8]. This suggests that EBV infection may be more prevalent in HSP patients. HSP patients with concurrent EBV infection may exhibit distinct clinical features compared to those without EBV infection. These features may include more severe skin manifestations, increased gastrointestinal symptoms, and a higher risk of renal involvement. EBV is known to modulate the immune response in the host. It can activate T cells and induce the production of various cytokines and antibodies [9]. The immune response triggered by EBV infection may potentially contribute to the development and progression of HSP. EBV infection may act as a triggering factor in individuals who are genetically predisposed to HSP. Some studies have suggested that EBV infection in HSP patients may be associated with a poorer prognosis, including an increased risk of renal complications and disease relapse [10,11]. However, more research is needed to validate these findings and determine the precise impact of EBV infection on the long-term outcomes of HSP. Since the exact pathophysiologic connection between the two remains poorly understood, this study aimed to investigate the impact of EBV infection on the development and prognosis of HSP and shed light on the underlying mechanisms.

Methodology

Participant baseline characteristics

The study included 120 children diagnosed with HSP who were admitted to the hospital between December 2020 and August 2022. Additionally, 100 healthy children who underwent physical examinations at the hospital outpatient clinic during the same period were selected as the control group.

The inclusion criteria were as follows. (1) Aged between 2 and 18 years. (2) Meeting the diagnostic criteria of HSP according to the 2013 evidence-based diagnostic and treatment recommendations for children's anaphylactoid purpura [7] as the initial diagnosis. Based on the recommendations, the clinical manifestations for children's anaphylactoid purpura include non-thrombocytopenic palpable purpura, primarily affecting the lower extremities and buttocks. Patients may experience arthralgia or arthritis, with joint pain or inflammation commonly involving the knees and ankles. Additionally, colicky abdominal pain may occur, potentially accompanied by gastrointestinal bleeding, vomiting, or diarrhea. Renal involvement is characterized by hematuria and proteinuria, and in more severe instances, may progress to nephrotic syndrome or acute kidney injury. Histological analysis via skin biopsy typically reveals leukocytoclastic vasculitis, often with IgA deposition in the walls of small blood vessels, particularly in the affected skin or renal tissue. (3) Absence of infectious symptoms and signs in the month prior to enrollment. (4) Being conscious without psychiatric diseases.

The exclusion criteria were as follows. (1) Presence of other diseases that can cause hematuria and proteinuria apart from allergic purpura. (2) Use of specific medications in the 3 months before enrollment (such as antibiotics, glucocorticosteroids, renal impairment drugs, immunosuppressants, or drugs affecting platelet function and coagulation). (3) Presence of other autoimmune diseases or drug allergic diseases. For example, antibiotics such as penicillins (e.g., amoxicillin, ampicillin) or cephalosporins (e.g., ceftriaxone, cefuroxime); glucocorticosteroids such as prednisone or dexamethasone; medications associated with renal impairment, including angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, lisinopril) or angiotensin II receptor blockers (ARBs) (e.g., losartan, valsartan); diuretics (e.g., furosemide, hydrochlorothiazide); non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen, diclofenac); and immunosuppressants such as methotrexate or mycophenolate mofetil, as well as medications affecting platelet function and coagulation, including aspirin, clopidogrel, or prasugrel. (4) Presence of coagulation disorders, thrombocytopenia, or a history of platelet dysfunction. (5) Presence of other causes of vasculitis or purpura. (6) History of EBV-related hematologic diseases.

There were 69 males and 51 females, aged between 2 and 17 years (mean age 7.84 ± 6.81 years) in the experimental group. The control group consisted of 21 males and 16 females, aged between 2 and 15 years (mean age 7.42 ± 5.50 years). There were no statistically significant differences between the two groups in terms of gender and age ($p > 0.05$). The study protocol was reviewed and approved by the Ethics Committee of the Tangshan Maternal and Child Health Hospital, and all enrolled subjects and their legal guardians were provided with informed consent forms to sign.

Detection of EBV infection using real-time fluorescence quantitative polymerase chain reaction (PCR)

The EBV *DNA polymerase* (*pol*) gene was utilized. This gene is frequently employed to measure viral load, particularly in determining the quantity of EBV DNA in blood or other clinical samples.

Two mL of fasting peripheral venous blood were collected from both groups of children (experimental group on the day of hospital admission, control group during physical examination) using aseptic techniques. One milliliter of whole blood was mixed with 1 mL of saline and added to a tube containing 500 μL of lymphocyte isolation solution. The mixture was centrifuged at 2000 rpm for 20 minutes, and the leukocyte layer was aspirated and transferred to a new centrifuge tube. The tube was then centrifuged at 12,000 rpm for 5 minutes, and the supernatant was removed. Next, 50 μL of DNA extraction solution was added to the precipitate, and the reaction was carried out at 100 °C for 10 minutes. After centrifugation at 12,000 rpm for 5 minutes, the supernatant was removed. Another 50 μL of DNA extract was added to the precipitate, and the reaction was carried out at 100 °C for 10 minutes. After centrifugation at 12,000 rpm for 5 minutes, the EBV-DNA load was determined using LightCycler real-time fluorescence quantitative PCR (Roche Applied Science, Penzberg, Germany). A load of $\geq 5 \times 10^3$/L was considered positive, while $< 5 \times 10^3$/L was considered negative.

Serological studies were added to assess EBV markers, including Epstein-Barr nuclear antigen 1 (EBNA1), viral capsid antigen (VCA), and EBV-specific IgM antibodies.

EBNA1 was identified as a key marker of latent EBV infection, expressed in all EBV-infected cells during the latent phase. Its presence was recognized as indicative of chronic or past infection, with the detection of EBNA1 antibodies (primarily IgG) suggesting prior infection and a potential latent stage. The presence of IgG antibodies against EBNA1 was associated with latent or past EBV infection, while their absence indicated no prior infection or an early stage of infection.

VCA was noted to be expressed during the acute phase of EBV infection, particularly in the early stages. Antibodies against VCA (both IgM and IgG) were utilized to differentiate between acute and recent infections. A positive VCA-IgM result was recognized as indicative of an acute or recent EBV infection, typically within the initial weeks. VCA-IgG was observed to appear later in the infection and persist for life, indicating past infection and subsequent immunity.

The presence of EBV-specific IgM antibodies was associated with acute primary infections or reactivation events, suggesting an active immune response. Detection of IgM antibodies was correlated with ongoing infection, and elevated levels were utilized to distinguish between acute infection and latent or reactivated states.

Serum samples were collected from both experimental and control groups for EBV serological analysis, alongside EBV DNA PCR. Enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assays were employed to test for EBV-specific antibodies, including VCA-IgM, VCA-IgG, and EBNA1-IgG.

The results were interpreted as follows: a positive VCA-IgM and negative VCA-IgG indicated acute or recent primary infection; a positive VCA-IgG and positive EBNA1-IgG suggested past infection with potential latency; and a positive EBNA1-IgG with negative VCA-IgM indicated latent infection, which could contribute to chronic conditions or disease exacerbations.

Thresholds for antibody levels were established. VCA-IgM was considered positive at a titer > 20 IU/mL, indicating acute EBV infection, while levels < 20 IU/mL suggested no recent infection. VCA-IgG was deemed positive at levels > 150 IU/mL, indicating chronic or past infection, with levels < 150 IU/mL suggesting no prior exposure. EBNA-IgG was recognized as positive at > 40 IU/mL, indicating prior exposure to EBV, while levels < 40 IU/mL indicated no prior exposure or a very recent infection that had not yet produced detectable levels of EBNA antibodies.

Measurement of renal function indexes and 24-hour urine protein quantitative testing

Peripheral venous blood was collected from children with HSP in a fasting state in the early morning. The blood was centrifuged at 2500 rpm for 20 minutes, and the levels of serum creatinine (Scr) and blood urea nitrogen (BUN) were determined using conventional spectrophotometric methods.

Urine samples from children with HSP were collected over a 24-hour period, and the level of urinary protein was measured using an automatic dry biochemical analyzer.

Prognosis

After discharge from the hospital, the children were regularly monitored and followed up through outpatient clinics or telephone. The recurrence of HSP symptoms

Table 1. Comparison of EBV infection in the two groups (n/%).

Group	n	EBV-DNA load positive (copies/mL)	EBNA1 (IgG) positive	VCA-IgM positive	VCA-IgG positive
Study group	37	15,714.29 ± 10,317.67	30 (81.08)	12 (32.43)	35 (94.59)
Control group	10	4285.71 ± 2477.59	5 (50.00)	1 (10.00)	9 (90.00)
t		12.024	2.684	5.248	6.314
p		0.02	0.01	0.04	0.21

EBV: Epstein-Barr virus; EBNA1: Epstein-Barr nuclear antigen 1; VCA: viral capsid antigen.

within 6 months was observed, and the occurrence of related symptoms after clinical improvement and treatment discontinuation was defined as recurrence. Based on the prognosis, the children were divided into the recurrence group (n = 48) and the non-recurrence group (n = 72).

Statistical analysis

The data was analyzed using the SPSS 29.0 software (IBM Corp, Armonk, NY, USA). Measurement data were presented as mean and standard deviation (x ± s), and t tests were used for comparison. Count data were presented as percentages (%), and compared with Chi-square tests. Statistical significance was set at $p < 0.05$.

Results

Comparison of EBV infection in the two groups

A total of 37 out of 120 children (30.83%) in the experimental group tested positive for EBV-DNA load, while 10 out of 100 children (10.00%) in the control group tested positive. The experimental group demonstrated a significantly higher positive rate of EBV-DNA load detection compared to the control group ($\chi^2 = 14.092$, $p < 0.05$), indicating a notable difference in the prevalence of EBV-DNA positivity between the two groups. Additionally, the study group exhibited a significantly higher rate of positivity for EBNA1 and VCA-IgM ($p < 0.05$). Although the positivity rate for VCA-IgG was higher in both groups, no significant difference was observed between the 2 groups ($p > 0.05$), as shown in Table 1.

Table 2. Comparison of EBV infection in children with different clinical phenotypes of HSP (n/%).

	n	EBV-DNA load	
		Positive	Negative
Simple type	15	4/26.67	11/73.33
Purpura abdominalis	30	15/50.00	15/50.00
Renal purpura	26	8/30.77	18/69.23
Purpura articularis	28	6/21.43	22/78.57
Mixed type	21	4/19.05	17/80.95
χ^2		15.398	
p		0.000	

EBV: Epstein-Barr virus; HSP: Henoch-Schönlein purpura.

Table 3. Comparison of renal function indexes and 24-hour urine protein quantification in children with HSP with different EBV infection conditions ($\bar{x} \pm s$).

	n	Scr (μmmol/L)	BUN (mmol/L)	Urine protein quantification (g/24hour)
EBV positive group	37	134.76 ± 15.34	12.42 ± 1.93	1.71 ± 1.12
EBV negative group	83	100.58 ± 14.76	7.56 ± 1.69	0.76 ± 0.31
t		11.574	13.916	7.168
p		0.000	0.000	0.000

EBV: Epstein-Barr virus; HSP: Henoch-Schönlein purpura: Scr: serum creatinine; BUN: blood urea nitrogen.

Relationship between EBV infection and clinical phenotype of children with HSP

The positive rate of EBV-DNA load test was significantly higher in children with abdominal HSP compared to those with articular and mixed phenotypes ($p < 0.05$), as shown in Table 2.

Comparison of renal function indexes and 24-hour urine protein quantification in children with HSP under different EBV infection conditions

The EBV-positive group exhibited significantly higher levels of serum Scr and BUN, as well as urine protein quantification, compared to the EBV-negative group ($p < 0.05$), as shown in Table 3.

Relationship between EBV infection and HSPN

Out of the 120 children with HSP, 38 (31.67%) developed HSPN; and among them, 32 (84.21%) had EBV infection. The positive rate of EBV-DNA load test was significantly higher in the HSPN group compared to the non-HSPN group ($p < 0.05$), as shown in Table 4.

Relationship between EBV infection and prognosis of children with HSP

The recurrence group exhibited a significantly higher positive rate of EBV-DNA load test compared to the non-recurrence group ($p < 0.05$), as shown in Table 5.

Table 4. Relationship between EBV infection and HSPN (n/%).

	n	EBV-DNA load	
		Positive	Negative
HSPN group	38	32/84.21	6/15.79
non-HSPN group	82	5/6.10	77/93.90
χ^2		74.293	
p		0.000	

EBV: Epstein-Barr virus; HSPN: Henoch-Schönlein purpura nephritis.

Detection of related antibodies in 173 EBV-DNA load negative children

Among the 173 children who tested negative for EBV-DNA load, 23.1% had recent EBV infection, 57.8% had past EBV exposure, and 19.1% had no evidence of EBV infection. The detailed results are presented in Table 6.

Table 5. Relationship between EBV infection and prognosis of children with HSP.

	n	EBV-DNA load	
		Positive	Negative
Recurrence group	48	31/64.58	17/35.42
Non-recurrence group	72	6/8.33	66/91.67
χ^2		42.729	
p		0.000	

EBV: Epstein-Barr virus; HSP: Henoch-Schönlein purpura.

Discussion

HSP is a prevalent autoimmune disease in children, characterized by inflammatory damage to the skin, joints, gastrointestinal tract, and kidneys. The potential role of EBV in autoimmune diseases has attracted significant interest. EBV, a member of the herpesvirus family, is linked to several conditions, including herpes simplex and lymphoproliferative disorders. While most EBV infections are asymptomatic, there is evidence suggesting that EBV can trigger abnormal immune responses in immunocompromised individuals, potentially contributing to the development of autoimmune conditions [8]. It is plausible that EBV infection may influence the onset or exacerbation of immune dysfunction in HSP. However, establishing a definitive causal relationship is complex due to the multifactorial nature of HSP, which is influenced by various environmental and genetic factors, making it difficult to ascertain whether EBV acts as a direct causative agent or merely a trigger in some cases. Additionally, the heterogeneity of HSP, with significant variations in clinical presentation and progression among affected children, complicates the generalization of EBV's role in the disease [12]. Despite these challenges, understanding the link between EBV infection and HSP could enhance early recognition and diagnosis, particularly in atypical cases, and inform prognostic strategies, enabling more tailored treatment approaches for affected children.

In this study, we employed real-time fluorescence quantitative PCR to detect EBV-DNA load in children with HSP and healthy children. Our findings revealed a significantly higher positive rate of EBV-DNA load detection in the experimental group (30.83%) compared to the control group (10%), aligning with previous research [9]. These results suggest that the prevalence of EBV infections in children with HSP may play a role in the pathogenesis of the disease. Our study indicates that the experimental group exhibits a significantly higher rate of EBNA1 positivity, suggesting that a majority of individuals in this cohort may harbor a latent EBV infection, which could potentially contribute to disease progression or chronic inflammation in HSP. Additionally, a higher rate of VCA-IgM positivity was observed, indicating that a greater proportion of individuals in the study group may be undergoing acute EBV infection or reactivation, which could be associated with the onset of HSP. While the rate of VCA-IgG positivity was elevated in both groups, no significant difference was found, suggesting that past EBV infections were prevalent across both the experimental and control groups.

Incorporating serological markers, including VCA, EBNA1, and IgM; along with viral load quantification; provides a more comprehensive understanding of EBV's role in HSP. By assessing both acute and latent infections, clearer conclusions can be drawn regarding whether EBV contributes to the triggering, exacerbation, or maintenance of the disease and how these mechanisms may interact with other factors such as immune responses, genetic predispositions, and environmental triggers [13].

HSP is characterized as an inflammatory vasculitic disease that primarily affects the skin, joints, gastrointestinal tract, and kidneys. In our study, the role of EBV infection in children with various clinical phenotypes of HSP were investigated [14]. Notably, a significantly higher positive rate of EBV-DNA load in children presenting with abdominal HSP compared to those with articular and mixed phenotypes were

Table 6. Antibodies associated with negative EBV-DNA load.

Profile	VCA IgM	VCA IgG	EBNA IgG	Interpretation	Number of children
Recent infection	Positive (> 20 IU/mL)	Negative (< 150 IU/mL)	Negative (< 40 IU/mL)	A recent or acute EBV infection	40 (23.12)
Past exposure	Negative (< 20 IU/mL)	Positive (> 150 IU/mL)	Positive (> 40 IU/mL)	Prior EBV infection and past exposure	100 (57.80)
No infection	Negative (< 20 IU/mL)	Negative (< 150 IU/mL)	Negative (< 40 IU/mL)	No EBV infection, either recent or past	33 (19.08)

EBV: Epstein-Barr virus; HSP: Henoch-Schönlein purpura; EBNA1: Epstein-Barr nuclear antigen 1; VCA: viral capsid antigen.

observed. This finding underscores a strong association between EBV infection and the abdominal subtype of HSP, suggesting potential variations in EBV-related immune modulation across different HSP subtypes.

HSP is characterized by small-vessel inflammation, which results in abnormal immune system activation, immune complex formation, and subsequent inflammation. These immune complexes can deposit in the kidneys, leading to renal impairment [10,15]. Viral infections, including EBV, have been implicated in the formation and exacerbation of immune complexes, contributing to kidney inflammation and dysfunction [11,12]. The findings of this study support this association, as significantly higher levels of Scr, BUN, and urine protein were noted in EBV-positive children with HSP compared to their EBV-negative counterparts. These results suggest that EBV infection may indirectly contribute to renal impairment in HSP through immune system activation. Furthermore, when comparing EBV-DNA loads between children with HSPN and those without, the analysis revealed a significantly higher positive rate in the HSPN group. This reinforces the connection between EBV infection and renal impairment in children with HSP [16–18]. Given these observations, we propose that active antiviral therapy should be considered in the clinical management of EBV-infected children with HSP to mitigate or delay renal damage.

Recurrence rates of HSP in children range from 10% to 30%, and multiple episodes of recurrence have been associated with an increased risk of kidney injury [13,14]. In this study, a significantly higher positive rate of EBV-DNA load test was observed in the recurrent group compared to the non-recurrent group. This suggests that EBV infection may contribute to or exacerbate the course of HSP, possibly through abnormal immune system activation resulting from EBV infection [15,19,20].

This study presents several important clinical implications based on the observed association between EBV infection and HSP. Firstly, healthcare professionals should incorporate EBV evaluation into their diagnostic protocols, particularly for children with abdominal manifestations, to facilitate early identification and timely management of at-risk patients. Secondly, the EBV-DNA load may serve as a valuable biomarker for risk stratification Children with higher levels could face increased risks of complications, such as HSPN, warranting closer monitoring and potentially more aggressive treatment. Additionally, the findings suggest that EBV infection has prognostic significance, as higher viral loads correlated with poorer renal function and elevated urine protein levels, indicating that ongoing monitoring of EBV could aid in predicting disease recurrence and guiding treatment decisions. Furthermore, understanding the role of EBV in HSP can inform targeted treatment strategies, allowing for more aggressive therapies in children at higher risk of complications to prevent disease progression and minimize long-term renal damage. Ultimately, integrating this knowledge into clinical practice can enhance patient care by enabling more accurate prognoses, personalized treatment plans, and effective monitoring strategies to detect early signs of recurrence or relapse.

This study has several important limitations that should be acknowledged. Firstly, while the detection methods for EBV employed are commonly used, they possess inherent limitations in sensitivity and specificity. For instance, PCR may not capture all cases of EBV infection, particularly during the latent phase when the viral load may be low or intermittent, leading to potential false negatives in subclinical infections. Integrating complementary methods such as serological tests for EBV-specific antibodies or more sensitive PCR techniques is recommended to enhance diagnostic accuracy.

Secondly, the study primarily focused on the association between EBV infection and the prognosis of HSP, but numerous confounding factors—including genetic predisposition, environmental influences, and co-infections with other pathogens—could also impact disease development and outcomes. A more comprehensive approach that accounts for these variables through stratified analyses or multivariable models would be beneficial in isolating the specific effect of EBV.

Additionally, the relatively short follow-up period of 6 months limited the ability to assess the long-term consequences of EBV infection on HSP outcomes, such as disease recurrence or chronic renal impairment. An extended follow-up would provide a more thorough understanding of EBV's role in long-term disease dynamics.

Moreover, while the study highlights the association between EBV infection and HSP prognosis, it lacks detailed mechanistic insights into how EBV contributes to HSP pathogenesis. Future research should incorporate immunological profiling and cytokine assays to elucidate the interactions between EBV and immune cells, thus clarifying the underlying immune mechanisms.

Finally, the use of a viral load cutoff of 5000

copies/mL to define EBV positivity may not be appropriate in all contexts, given EBV's ability to establish latent infections at lower viral loads. A more nuanced assessment that considers both viral load and serological markers of past infection would provide a clearer picture of the infection status and its implications for HSP development and prognosis.

Conclusions

A potential association between EBV infection and the occurrence and prognosis of HSP was observed. EBV infection was frequently detected in children with HSP and was correlated with clinical features, renal damage, and disease outcomes.

However, the study had limitations, including a small sample size, retrospective observational design, and limited consideration of other contributing factors. Future research directions should focus on elucidating the underlying pathogenic mechanisms, conducting large prospective studies with long-term follow-up, and evaluating the role of EBV infection in HSP treatment strategies.

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of the Tangshan Maternal and Child Health Hospital, and all enrolled subjects and their legal guardians were provided with informed consent forms to sign.

Data availability

All data generated or analyzed during this study are included with this article. Further enquiries can be directed to the corresponding author.

Authors Contributions

ZZ: study concepts and design: definition of intellectual content: literature research: clinical studies: experimental studies: manuscript preparation and editing; YZ: guarantor of integrity of the entire study: manuscript review; JH: data analysis; RR: data acquisition; GL and JY: statistical analysis. All authors read and approved the final manuscript.

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Conflict of interests

No conflict of interest is declared.

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