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Prognosis of EBV Infection in Children with Tonsillitis

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Determining the prognosis of Epstein-Barr virus (EBV) infection with in children with tonsillitis.
Methods: Totally 102 children with chronic tonsillitis admitted to our hospital between January 2017 and March 2019 were selected. Among them, 52 children with EBV infection were assigned to a case group, and the other 50 without EBV infection to a control group. All children were given targeted therapy. Then the two groups were compared in efficacy, defervescence time, alleviation time of tonsillar enlargement and pharyngalgia after therapy, immune function-associated indexes and inflammatory factor-associated indexes before and after therapy, incidence of adverse reactions during therapy, and recurrence times during therapy and 1-year follow-up.
Results: Compared with the case group, the control group showed notably better efficacy, experienced notably shorter alleviation time of tonsillar enlargement and pharyngalgia, and presented better improvement in immune function and inflammation (all $P<0.05$). Additionally, the two groups were not greatly different in the incidence of adverse reactions ($P>0.05$), while the control group experienced notably less times of recurrence during therapy and 1-year follow-up ($P<0.05$).
Conclusion: EBV infection will compromise the efficacy on children with tonsillitis and take its toll on their prognosis, so it is imperative to adopt a targeted and individualized therapeutic regimen for children with both diseases.

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1. INTRODUCTION

Epstein-Barr virus (EBV) is highly infectious as it can spread through droplets, saliva and blood, and children are prone to it due to their imperfect immune function [1], as many other infection diseases which are related to immune system dysfunction [2-5]. Additionally, EBV is DNA virus susceptible to upper respiratory tract, is discovered to be bound up with tonsillitis [6]. Tonsillitis is a pervasive condition in children, which is caused by multiple factors like EBV infection. Passive therapy of it probably induces various complications and even systemic infections, which is blindingly unfavorable for children's growth [7].

In childhood, besides EBV infection, bacterial infection such as Streptococcus and Staphylococcus might also give rise to tonsillitis, and their low immune function also make them prone to repeated respiratory infections [8-11]. Now, tonsillitis is primarily treated by antibacterial therapy or immune system regulation [12]. Whereas, tonsillitis might be induced by EBV infection, but specific drugs against EBV are still scarce. The frequently applied drug for it is only interferon that boasts of broad-spectrum antiviral function as a multifunctional active protein [13].

Similar findings have shown the effect of Epstein-Barr virus on children's tonsils. These studies show that children's tonsils can be infected by EBV. Such colonies may also be associated with the pathogenesis of recurrent tonsillitis and lead to chronic disease [14,15]. Another study shows that EBV resides continuously in the nasopharyngeal region after the initial infection and may become an advanced disease [16].

However, for children with EBV infection-induced tonsillitis, whether the infection impacts the efficacy of subsequent tonsillitis therapy on them is still under investigation.

We compared the efficacy on children with both tonsillitis and EBV infection and those with only tonsillitis, and determined the impact of EBV infection on the efficacy on tonsillitis for timely improvement of therapeutic regimen for children with both tonsillitis and EBV infection.

2. MATERIALS AND METHODS

2.1 Patient

In this clinic practice study Totally 102 children with chronic tonsillitis admitted to our hospital between January 2017 and March 2019 were selected. Among them, 52 children with EBV infection were assigned to a case group, and the other 50 without EBV infection to a control group. All children were given targeted therapy.

Eligible patients with chronic tonsillitis were included in the study. For the case group, except the above criteria, the copy number prompted in DNA determination of EBV among pharyngeal secretions >1.0×103/mL should be considered. Approval was attained from the ethics committee of our hospital for the study, and children' guardians signed an informed consent document. Exclusion criteria were confirmed patients with lower respiratory tract infection, patients who had received therapy of other drugs recently, patients allergic to drugs utilized in our study, and those with comorbid malignancies, immune system problem, or congenital heart disease.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were confirmed patients with chronic tonsillitis(Recurrent tonsillitis is described as more than seven episodes in one year, more than five episodes annually for more than two years, more than three episodes annually for more than three years, or two weeks or more of lost school in one year due to tonsillitis), patients with clinical manifestations like headache, fever(presence of temperature >38.30C), sore throat, cervical lymphadenopathy (tender lymph nodes or >2 cm), tonsillar exudates, foreign body sensation and anorexia, and those with unilateral or bilateral tonsillar enlargement that was accompanied by pus sometimes. In addition, PCT positive for Epstein-Barr virus was one of the inclusion criteria in the case group. Children who underwent tonsillectomy for obstructive symptoms alone and children who received antibiotics at least one month prior to surgery and if they do not want to continue, they will be excluded from the study.

2.3 Treatment

Both groups were given symptomatic therapy after admission, primarily including antipyretic,

anti-asthmatic, expectorant and anti-infective therapy.

Specifically, for children in the control group, each child was given 100 mg/ (kg/d) amoxicillin/potassium clavulanate. The amoxicillin/potassium clavulanate was used via intravenous injection with 0.9% sodium chloride injection two times. For children in the case group, each child was given recombinant human interferon α1b injection through intramuscular injection 1 time/d within the first 5 days and then once every other day 5 μg/ (kg/time) injection for children within 2 years old and 10 μg/ (kg/time) injection for children over 2 years old. Children with cough and expectoration were given budesonide inhalation suspension that was utilized with 1.5 mL normal saline by 0.6 mg each time via oxygen atomizing inhalation 2 times/day and 10 min/time, and the therapy was stopped at the alleviation of symptoms. Children with high fever were given oral administration of ibuprofen suspension, 3 mL suspension for children between 2-3 years old and between 12-14 years old, 5 mL suspension for children between 4-6 years old and between 16 -20 years old, and 8 mL suspension for children between 7-9 years old and between 22-26 years old. Once their body temperature did not drop after such therapy, the ibuprofen suspension can be repeatedly given every 4-6 hours.

2.4 Outcome

The efficacy evaluation criteria were Markedly effective (Complete disappearance of clinical symptoms), Effective (Amelioration of clinical symptoms), Ineffective (No amelioration of clinical symptoms). Total effective rate was calculating by (Markedly effectively treated patients + effectively treated patients) / total number of patients*100% [17].

We compared the defervescence time and alleviation time of tonsillar enlargement and pharyngalgia after therapy between the two groups. We collected 3 mL fasting venous blood (FVB) from each participant at early morning before and after therapy, and quantified immune function-associated indexes in them via flow cytometry for understanding the changes of immune function of both groups. The indexes included CD4+ and CD8+, and calculated CD4+/CD8+ and quantified IL-6 and TNF-α via ELISA. We recorded and compared the incidence of adverse reactions (headache, nausea and vomiting, liver function injury, and skin allergy) the times of recurrence during therapy and 1-year follow-up between the two groups.

(Methods such as in situ hybridization, polymerase chain reaction (PCR), and immunochemistry have been used to study the pathogenesis of the EBV)

2.5 Statistical Analyses

Our study used SPSS19.0 for statistical analyses of acquired data and GraphPad Prism 8 for figure drawing. Additionally, our study applied the chi-square test for comparison of enumeration data, and the independent t test for multi-group comparison of measurement data presented as the mean ± SD. $P < 0.05$ denotes a notable difference.

3. RESULTS

3.1 Comparison of General Data

The results showed that 53.85% of case group were male and the mean age of patients was 8.61 and in the control group, 60% were male and the mean age was 9.24 years. No significant difference was observed in terms of demographic variables (P>0.05).

As shown in Table 1, the two groups were similar in gender, mean age, mean body mass index, Course of acute attack, The first attack, Liver function-associated index, Total serum protein, Glutamic-pyruvic transaminase and Total bilirubin.

3.2 Efficacy on Tonsillitis

The case group had 20 patients treated markedly effectively, 18 treated effectively, and 14 treated ineffectively, while the numbers in the contorl group were 35, 14, and 1, respectively. Therefore, the Reg group showed a notably higher total effective rate than the Inf group and There was a statistically significant difference between the case group and the Control group (P<0.05) (Table 2).

3.3 Defervescence Time and Alleviation Time of Tonsillar Enlargement and Pharyngalgia after Therapy

The control group experienced notably shorter defervescence time and alleviation time of tonsillar enlargement and pharyngalgia than the case group. There was a statistically significant difference between the case group and the Control group (P<0.05) (Table 3).

Table 1. General data

Factor	Case (n=52)	Control (n=50)	P-value
	n,(%)	n,(%)	
Gender			0.53
Male	28 (53.85)	30 (60.00)	
Female	24 (46.15)	20 (40.00)	
Age (years)			0.64
≥6	31 (59.62)	32 (64.00)	
<6	21 (40.38)	18 (36.00)	
BMI (kg/m2)	15.32±1.11	15.41±1.15	0.68
Course of acute attack (days)	8.45±1.26	8.31±1.34	0.58
The first attack			0.99
Yes	27（51.92）	26(52.00)	
No	25（48.08）	24(48.00)	
Liver function-associated index			
Total serum protein (g/L)	65.21±2.18	65.13±2.22	0.85
Glutamic-pyruvic transaminase (μmol/L)	27.39±3.16	27.27±3.25	0.85
Total bilirubin (μmol/L)	11.05±2.17	11.13±2.21	0.85

Table 2. Evaluation of clinical efficacy on the two groups

Efficacy	Case (n=52)	Control (n=50)	P-value
	n,(%)	n,(%)	
Markedly effective	20 (38.46)	35 (70.00)	0.03
Effective	18 (34.62)	14 (28.00)	0.01
Ineffective	14 (26.92)	1 (2.00)	0.001
Total effective rate	38 (73.08)	49 (98.00)	<0.001

Table 3. Comparison of defervescence time and alleviation time of tonsillar enlargement and pharyngalgia after therapy between the two groups

Item	Case (n=52)	Control (n=50)	P-value
	n,(%)	n,(%)	
Defervescence time	4.62±1.11	3.02±0.76	<0.001
Alleviation time of pharyngalgia	4.23±1.15	3.15±0.86	<0.001
Alleviation time of tonsillar enlargement	7.51±1.32	5.14±1.12	<0.001

3.4 Changes of the Immune Function

Before therapy, no difference was finally revealed in level of CD4+, CD8+, and CD4+/CD8+ between those with Case and the control group (P>0.05), while after therapy, both groups showed notably increased CD4+ and CD4+/CD8+ and notably decreased CD8+, and the increase and decrease in the Reg group were both more notable (P<0.05) (Fig. 1).

3.5 Changes in Serum Inflammatory Factors

Before therapy, no difference was finally revealed in levels of serum IL-4 and TNF-α between those with Case and the control group(P>0.05), while after therapy, the levels of them in both groups decreased notably, and the decrease in the control group was more remarkable (P<0.05) (Fig. 2).

3.6 Adverse Reactions in both Groups During Therapy

After therapy, the case group presented an incidence of adverse reactions of 7.69%, with headache, nausea and vomiting, liver function injury and skin allergy in 1, 1, 0 and 2 patients, while the control group presented an incidence of adverse reactions of 8.00%, with headache, nausea and vomiting, liver function injury and skin allergy in 2, 1, 0 and 1 patients, so the two groups were not statistically different in this aspect (P>0.05) (Table 4).

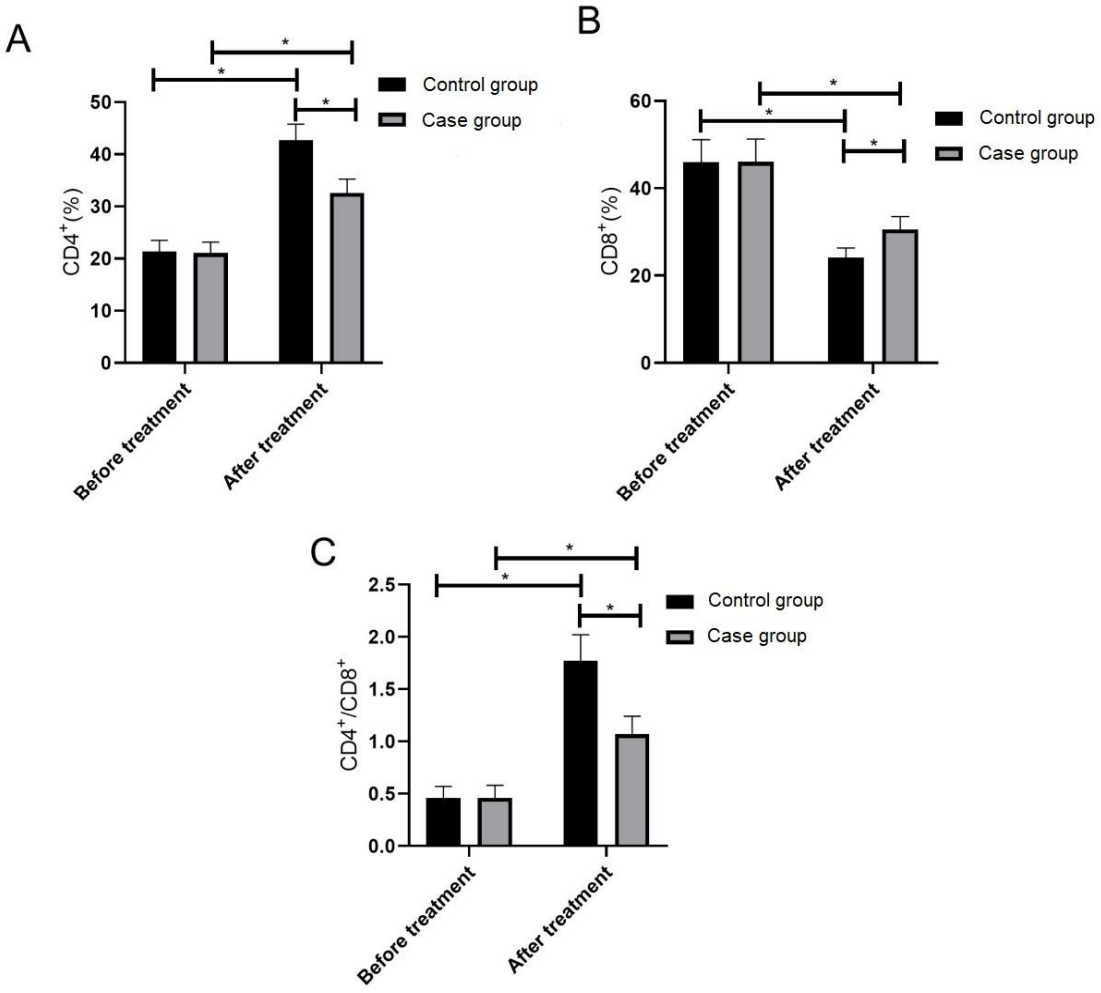

Fig. 1. Changes in immune function of the two groups before and after treatment. A, CD4+; B, CD8+; C, CD4+/CD8+

** P<0.05*

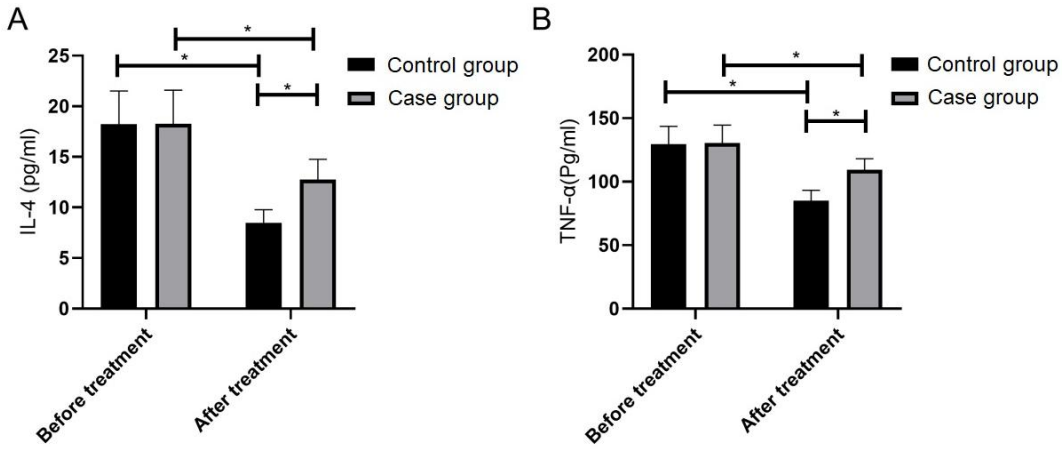

Fig 2. Changes in serum inflammatory factors of both groups; A, IL-4; B, TNF-α

**P<0.05*

Table 4. Comparison of the incidence of adverse reactions between the two groups

Evaluation of adverse reactions	Case (n=52)	Control (n=50)	P-value
	n,(%)	n,(%)	
Headache	1 (1.92)	2 (4.00)	0.18
Nausea and vomiting	1 (1.92)	1 (2.00)	0.22
Liver function injury	0	0	--
Skin allergy	2 (3.85)	1 (2.00)	0.28
The incidence of adverse reactions	4 (7.69)	4 (8.00)	0.954

3.7 Times of Recurrence during Therapy and 1-Year Follow-Up

During therapy, the control group experienced notably less times of recurrence than the case group ((0.43±0.15) times vs. (1.84±0.31)), and during the 1-year follow-up, the control group also experienced notably less times of recurrence than the case group (2.71±0.63) times vs. (6.92±1.85) times). There was a statistically significant difference between the case group and the Control group (both P<0.05) (Table 5).

4. DISCUSSION

Our study treated children with both tonsillitis and EBV infection and those with tonsillitis alone, and compared the efficacy on them. As a result, after symptomatic therapy, children infected with EBV presented notably superior efficacy to these not infected with it, indicating the hindering of EBV infection on recovery of children with tonsillitis. Our study also finding that the control group experienced notably shorter defervescence time and alleviation time of tonsillar enlargement and pharyngalgia than the case group. The results imply the clinical symptoms and signs of children without EBV infection can be alleviated more easily and the clinical efficacy on them was more powerful. Endo et al. Showed in parallel studies that children with EBV are associated with recurrent tonsillitis and that treatment is important [18].

Other similar findings show that depending on the cause of the infection, different treatments are prescribed for the treatment of tonsillitis and attention to the identification of the infectious agent has a significant effect on the therapeutic effectiveness. For instance, bacterial infection-induced tonsillitis is primarily treated via antibiotics clinically [19,20], although, EBV induced tonsillitis should be given antiviral therapy [21]. Recent findings have shown that EBV is asymptomatic in many children and varies in pathogenicity depending on the degree of virus infection [22].

We compared IL-4, TNF-α, CD4+, and CD8+ in the two groups before and after therapy, and found more notable amelioration in inflammatory factors and immune function-related indexes in the control group than that in the case group. The data imply the better recovery of children without EBV from tonsillitis.

Recent similar studies have shown that the secretion of cytokines secreted by CD4 + T lymphocytes in Epstein-Barr is altered [23]. In 2020, Geißler et al. Showed that stimulation of T cells in patients with tonsillitis increased the concentration of cytokines released in the tonsils and blood, as well as in various forms of inflammation and non-inflammatory tissue. Stimulation increases the pro-inflammatory cytokines TNF-α, IFN-γ and IL-2 more than the anti-inflammatory cytokines IL-4 and IL-10 in tonsil and blood samples in RAT, PTA and non-inflammatory samples. The blood of patients with tonsillitis showed higher levels of proinflammatory cytokines compared to the samples of non-inflammatory patients [24]. The present study has also reported this finding.

Other similar findings have reported that Tonsillitis primarily results from infection due to low immune function, so for children with it,

Table 5. Times of recurrence during therapy and 1-year follow-up in the two groups

Times of recurrence	The infection group (n=52)	The routine group (n=50)	P-value
During the therapy	1.84±0.31	0.43±0.15	<0.001
During 1-year follow-up	6.92±1.85	2.71±0.63	<0.001

recovery of immune function is crucial in improving efficacy [25]. According to previous research, immune dysfunction of T lymphocytes in children with tonsillitis is continuous, and The cells, crucial in allergic inflammation of the immune system, can regulate acute and chronic allergic inflammation by reducing various cytokines, and the function of The cells mainly depends on inflammatory cytokines [26,27].

Finally, we compared the incidence of adverse reactions and recurrence rate during therapy and 1-year follow-up between the two groups. The two groups were not greatly different in the incidence of adverse reactions, which showed the safety of drug treatment in both groups.

As prior studies demonstrated, after invading the human body, viruses form various independent mechanisms to escape the tracking and monitoring of the immune system, and the host cells are unable to remove these viruses, so that they are latent in the body or proliferate at a low level, and keep a relative balance with the host, but decline in immune function of the body could make them replicate and activate [28]. Moreover, viruses can easily lurk in tonsils. If they are not eliminated completely, even if the symptoms of children are alleviated, once their immunity decline, the disease will recur again, which is not conducive to the prognosis of children [29]. As a result, paying attention to increasing the immune system of children can reduce the severity of tonsillitis in children by reducing the population of pathogens in the body.

5. CONCLUSION

EBV infection compromise the efficacy of children with tonsillitis and take its toll on their prognosis, so it is imperative to adopt a targeted and individualized therapeutic regimen for children with both diseases. This study has limitation, for instance, we cannot further determine which treatment scheme is more effective for children with EBV infection, and it need more investigation on this in future research.

CONSENT AND ETHICAL APPROVAL

Approval was attained from the ethics committee of our hospital for the study, and children' guardians signed an informed consent document.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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