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ORIGINAL ARTICLE

Performance of Clinical Features, Acute Phase Reactants and Group A Streptococcus Rapid Test in Evaluation of the Etiologic Agents for Tonsillopharyngitis in Children

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SUMMARY

Background: **It is important to determine the causative agent of tonsillopharyngitis in children, whether group A beta-hemolytic streptococcus (GABHS) or another agent. In this study, we investigated epidemiological data and clinical symptoms and also evaluated the performance of group A streptococcus rapid test (GASRT) and acute-phase reactant tests in distinguishing viral and bacterial agents by performing assays for GABHS and for Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV-1), adenovirus, and enterovirus, from samples obtained from children with tonsillopharyngitis.**

Methods: **One hundred fifty pediatric patients were evaluated for complaints of body fever, sore throat, headache, cough, and abdominal pain. Identification of GAS isolates was performed using culture, a rapid test for GAS detection, and a L-pyrrolidonyl arylamidase (PYR) test, as well as a latex agglutination test and the Vitek 2 automated system when needed. The complete blood count (CBC), neutrophil/lymphocyte ratio (NLR), anti-streptolysin O (ASO), sedimentation, and high-sensitivity C-reactive protein (hs-CRP) were quantified. Molecular analyses were performed for EBV, adenovirus, enterovirus, and HSV-1 detection using the Anatolia Montania 4896 RT PCR platform.**

Results: **Throat cultures were positive for GABHS in 11 (7.3%) children. The absence of coughing and the presence of painful cervical LAP were significantly higher in the GABHS-positive group. GASRT was positive in 14 (9.2%) children; 10 (90%) of the 11 GABHS culture-positive cases were also positive for GASRT. In the GABHS-positive group, there was no difference in sedimentation or ASO values compared with GABHS-negative group. When the viral agent-positive group was compared with the group where no agent was found, WBC, NLR, and CRP were significantly higher, and PLT was significantly lower.**

Conclusions: **Causative agent of acute tonsillopharyngytis in children is usually a virus. EBV was the most common viral agent in tonsillopharyngitis. The absence of coughing and the presence of painful cervical lymphadenopathy can be important indicators in the diagnosis of GABHS positivity. GASRT is a highly reliable assay. WBC, NLR, and CRP are higher in GABHS-positive patients.**

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KEY WORDS

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INTRODUCTION

Tonsillopharyngitis (TF) is one of the most common diseases in children; it is seen in about 6 - 8% of the outpatient population worldwide [1,2]. Viruses are the most common causative agents (> 70%), and group A beta-hemolytic streptococcus (GABHS) is responsible for 10 - 30% of cases [3,4]. It is important to distinguish whether GABHS or another agent is the causative agent in TF due to suppurative and non-suppurative complications and the need for antimicrobial therapy [5]. However, there are some difficulties in distinguishing causes according to clinical and epidemiologic data in children [4,6]. In children, clinical findings in GABHS TF have some similarities to those of other causative agents, especially viruses [1,5]. This decreases the reliability of clinical scores used in diagnosis [7,8]. Throat culture remains the gold standard for GABHS diagnosis. However, its role in early diagnosis and therapy is restricted because of slow results and positive results in carriers [9]. The group A streptococcus rapid test (GASRT) and acute-phase reactants are important in early diagnoses [5,10]. *Arcanobacterium hemolyticum* is a rarely seen bacterial agent in TF [11].

Although other descriptive clinical findings can be valuable in some viral TF cases, some findings are similar to those of GABHS TF [9]. Fever, exudative pharyngitis, and cervical lympadenitis can be seen in infection with Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV-1), and adenovirus, as well as in GABHS infection. Herpangina is diagnostic for enterovirus, but it is not seen in all cases in children [12,13]. The agents that show similar clinical findings to GABHS infections are seen frequently, which limits the usefulness of the adult guidelines in children [14,19].

It has been reported that 50 - 70% of children with TF are given antibiotic treatment, even in countries where post-streptococcal complications are rarely observed, leading to serious problems with antibiotic resistance. Thus, there is a need for studies on early diagnosis to guide treatment [2,15-17].

The ability to determine the clinical and laboratory characteristics of viruses that cause symptoms similar to those of GABHS infection will assist in early diagnosis and in treatment decisions. In this study, we investigated epidemiological data, clinical symptoms, and the performance of GASRT and acute-phase reactant tests in distinguishing viral and bacterial agents by performing assays for GABHS and for EBV, HSV-1, adenovirus, and enterovirus, which show clinical similarities to GABHS infection, using throat swab samples from children with tonsillopharyngitis.

MATERIALS AND METHODS

Patients and study design

Participants were 150 pediatric patients (2 - 17 years old) who were admitted to the Sakarya University Training and Research Hospital Pediatric Emergency Service in Sakarya, Turkey, complaining of a sore throat and who were diagnosed with tonsillopharyngitis. Informed consent forms were obtained from patients and their relatives. At the time of the hospital admission, patients were evaluated for complaints of body fever, sore throat, headache, cough, and abdominal pain. Tonsillopharyngitis was diagnosed with one or more of the following symptoms: sore throat, fever, swallowing difficulty, tonsillar hyperemia, crypt hypertrophy or exudate, soft palate petechiae, and cervical lymphadenopathy. Swab samples were taken from both tonsils and the posterior wall of the pharynx with two different sterile swabs for throat culture, GASRT, and molecular virus identification. GASRT, throat culture, and complete blood count (CBC) were performed. The neutrophil/lymphocyte ratio (NLR), anti-streptolysin O (ASO), sedimentation, and high-sensitivity Creactive protein (hs-CRP) were quantified. Furthermore, molecular tests were used to determine the presence of EBV, adenovirus, HSV-1, and enterovirus.

Bacterial culture and identification

Throat swab specimens were processed using standard procedures. Throat cultures were obtained by swabbing both tonsils and the posterior pharynx with a rayon-tipped swab (Becton Dickinson, USA). The swab was then placed in Amies medium without charcoal, transported to the laboratory, and plated within 2 hours. The swab was plated on 5% sheep blood agar; the agar was stabbed, and bacitracin and trimethoprim sulfamethoxazole disks (Becton Dickinson, USA) were placed in the primary streak. The plates were incubated at 35 - 37°C in 5% CO_2 and were examined at 24 and 48 hours. β-Hemolytic colonies were subcultured, isolated, and then typed. All throat swabs were obtained by one of two investigators; the processing of throat cultures was overseen by one specialist.

Bacterial identification focused on group A β-hemolytic streptococci. Identification of GAS isolates was performed using bacitracin (0.004 U) and trimethoprim sulfamethoxazole (1.25/23.75 μg) disks (Becton Dickinson, USA), a rapid test for GAS detection, and a L-pyrrolidonyl arylamidase (PYR) test (Becton Dickinson, USA), as well as a latex agglutination test (Plasmatec Lab Products, Ltd UK) and the Vitek 2 automated system (bioMerieux, France) when needed. Blood agar was used for *Arcanobacterium haemolyticum* culturing.

GAS rapid antigen test

The Strep A Rapid Test cassette (Hangzhou Biotest, Germany), a qualitative immunoassay to detect GAS antigens from a throat swab, was used for the GAS rapid test.

Molecular studies

Molecular analyses were performed for EBV, adenovirus, enterovirus, and HSV-1 detection with swab samples from pediatric patients with TF after GAS was ruled out. DNA extraction from swab samples was carried out on tonsillar membranous exudate using the Magnesia Extraction Kit and a Nucleic Acid Extraction robot (Magnesia 2448, Anatolia Geneworks, Turkey). Real-time PCR testing was performed in accordance with the manufacturer's protocol with a Montania 4896 RT PCR platform (Anatolia Geneworks) for the detection of EBV, adenovirus, enterovirus, and HSV-1. The Bosphore EBV Quantification Kit v1 was used to detect EBV, the Bosphore Adenovirus Detection Kit v1 to detect adenoviruses, the Bosphore Enterovirus Detection Kit v1 to detect enteroviruses, and the Bosphore HSV 1-2 Genotyping Kit v1 (all Anatolia Geneworks) to determine the HSV type 1. Results were obtained automatically using the software of the real-time PCR machine.

Statistical analysis

Descriptive statistics were used to examine the general features of the participants. The Kolmogorov-Smirnov test was used to assess the distribution of numerical variables. Those variables with normal distributions are presented as means ± standard deviations, and those with non-normal distributions as medians (minimum-maximum). Categorical variables are indicated as number (n) and percentage (%). Student's *t*-test, the Mann-Whitney *U*-test, ANOVA, and the Kruskal-Wallis *H*-test were used to compare groups. Groups defined by categorical variables were compared using χ^2 or Fisher's exact tests. Receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity and specificity of laboratory parameters for predicting the presence of GABHS. A p-value < 0.05 was considered to indicate statistical significance in all analyses. The SPSS software (ver. 20 for Windows; IBM SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Step-wise multivariable logistic regression analysis was used to identify independent predictors of GABHS risk.

RESULTS

In total, 150 children aged 2 - 17 years (median age, 7.3 years) with acute exudative TF were enrolled in this study, including 79 (53%) boys and 71 (47%) girls. Throat cultures were positive for GABHS in 11 (7.3%) children. *Arcanobacterium haemolyticum* was not detected in any patient. EBV was the most common viral agent (50%), and in 52 (34%) cases none of the agents tested were detected. GABHS and viral agents isolated from patients are listed Table 1.

Demographic data, clinical findings, and laboratory data for GABHS- and virus-positive cases and for cases where no agent was detected are shown in Table 2. The absence of coughing and the presence of painful cervical LAP were significantly higher in the GABHS-positive group. GASRT was positive in 14 (9.2%) children; 10 (90%) of the 11 GABHS culture-positive cases were also positive for GASRT. However, in four GASRT-positive patients, there was no positive result in GABHS culturing. The GASRT sensitivity and specificity in GABHS diagnosis were 90% and 97%, respectively. In the GABHS-positive group, there was no difference in sedimentation and ASO values compared with the viral agent-positive group and the group where no agent. When the GABHS-positive group was compared with the viral agent-positive group and the group where no agent was found, WBC, NLR, and CRP were significantly higher.

The risk of GABHS positivity in cases with painful cervical LAP was increased 14.920 fold; in cases with no cough, by 6.253 fold; and in cases aged 7 - 17 years, by 2.973 fold (Table 3).

ROC analyses and the determination of optimum cutoff values were performed to assess the power of WBC, NLR, CRP, ASO, and sedimentation values in a GABHS diagnosis (Figure 1). The sensitivity and specificity of sedimentation and ASO values were low.

DISCUSSION

It is important to determine the causative agent of TF in children, whether GABHS or another agent [5]. However, even experienced pediatricians have difficulty distinguishing GABHS and viral agents using only clinical findings and epidemiological data, and this affects treatment and antibiotic use [2,4,6,15-17]. Increasing antibiotic use points to the importance of distinguishing between bacterial and viral infection with an assay that is fast and readily applicable, has high sensitivity and specificity, and is inexpensive.

Some studies have reported GABHS rates between 12 and 29% in febrile exudative tonsillitis cases [6,18-20]. Sharland et al. reported that GABHS positivity was 2% in children with acute pharyngitis [21]. In 2016, Cohen et al. reported GABHS rates between 20 and 40% in a Cochrane analysis [22]. In our study, the GAS rate was 7.3% in children admitted with throat pain and rash. No bacterial agent other than GABHS was found. In particular, *Arcanobacterium haemolyticum* was not found in any patient. Taken together, the data presented here are consistent with previous literature. The low rate of GABHS is important. One reason for the low rates in our study may be that the patient population in other studies comprised patients with exudative tonsillitis, whereas we included children who presented with a sore throat and rash. When conducted with the correct technique, the sensitivity of the GABHS assay with a single throat swab is 90 - 95% [23,24]. Furthermore, the high rate of antibiotic use in Turkey suggests that it may have resulted in a decrease in the spread of GABHS. Although some studies have reported different rates of

Table 1. GABHS and viruses isolated from children with tonsillopharyngitis.

Agents	n	%
GABHS positive	11	7.3
EBV	75	50
HSV-1	16	10.7
Adenovirus	13	8.7
Enterovirus	8	5.3
GABHS + EBV	5	3
More than a virus	20	13
No agent detected	52	34

EBV - Ebstein-Barr virus, GABHS - group A beta hemolytic streptococcus, HSV-1 - herpes simplex virus type 1.

Table 2. Demographic characteristics, clinical and laboratory findings in children with acute tonsillopharyngitis by GABHS positive, virus positive and the group where no agent was found.

Clinical characteristics	GABHS positive group (%) (n = 11)	Virus positive group (%) (n = 87)	Group no agent found (%) (n = 52)	p
Gender				
Male	45	52	56	0.794
Female	55	48	44	
Age (years)				
2 - < 5	18	43	35	0.241
5 - < 17	82	57	65	
Fever (≥ 38°C)				
Yes	73	47	52	0.271
No	27	53	48	
No cough				
Yes	73	26	29	**0.007**
No	27	74	71	
Headache				
Yes	45	35	30	0.622
No	55	65	70	
Abdominal pain				
Yes	36	38	30	0.692
No	64	62	70	
Painful cervical lymphadenopathy				
Yes	90	49	60	**0.010**
No	10	51	30	
Tonsillary exudate				
Yes	45	60	71	0.331
No	55	40	29	
GASRT				
Positive	10	1.1	5.8	**< 0.001**
Negative	1	98.9	94.2	
WBC (mm^3) (mean, SD)	21.85 (6,12) [a, b]	14.23 (5.92) [c]	14.742 (5.09) [c]	**0.020**
NLR (median, min - max)	11.96 (6.32 - 19.51) [a, b]	4.53 (0.28 - 22.14) [c]	5.03 (0.96 - 19.44) [c]	**0.003**
hsCRP (mg/dL) (median, min - max)	7.23 (3 - 78) [a, b]	3.83 (1 - 29) [c]	3.50 (1 - 15) [c]	**0.049**
ASO (IU) (median, min - max)	272.00 (47.5 - 1070.0)	87.50 (47.50 - 746.0)	121.0 (47.50 - 1410.0)	0.388
Sedimentation (mm/hour) (median, min - max)	26.50 (16 - 52)	26.50 (7 - 76)	28.50 (4 - 61)	0.863

ASO - anti-streptolysin O, GASRT - group A streptococcus rapid test, hsCRP - high-sensitivity C-reactive protein, NLR - neutrophil/ lymphocyte ratio, WBC - white blood cell. Values were represented as n, %, mean (SD), median (min-max). P-values < 0.05 were considered to indicate statistical significance. [a] - Difference according to virus positive group, [b] - Difference according to the group where no agent was found, [c] - Difference according to GABHS positive group.

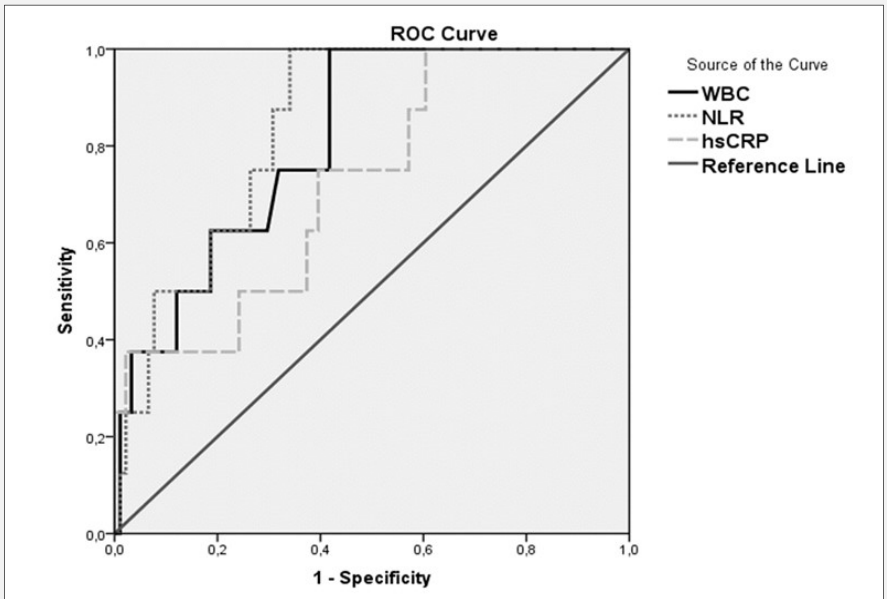
Table 3. Demographic characteristics and clinical signs predicting GABHS in children with acute tonsillopharyngitis.

	n = 150	GABHS positive (n = 11)	GABHS negative (n = 139)	p-value	OR and 95% CI
Gender					
Male [a]	**79**	**5**	**74**		**1**
Female	**71**	**6**	**65**	**0.185**	**0.353 (0.076 - 1.643)**
Age (year)					
2 - < 5 [a]	**49**	**2**	**47**		**1**
5 - < 17	**101**	**9**	**92**	**0.207**	**2.973 (0.547 - 16.151)**
Cervical lymphadenopathy					
No [a]	**75**	**1**	**74**		**1**
Yes	**75**	**10**	**65**	**0.020**	**14.920 (1.527 - 145.812)**
No cough					
No [a]	**46**	**8**	**38**		**1**
Yes	**104**	**3**	**101**	**0.016**	**6.253 (1.412 - 27.684)**
Headache					
No [a]	**107**	**6**	**101**		**1**
Yes	**43**	**5**	**38**	**0.611**	**1.502 (0.314 - 7.188)**
Fever (≥ 38°C)					
No [a]	**74**	**3**	**71**		**1**
Yes	**76**	**8**	**68**	**0.232**	**0.364 (0.069 - 1.908)**
Tonsillary exudate					
No [a]	**95**	**6**	**89**		**1**
Yes	**55**	**5**	**50**	**0.670**	**0.723 (0.163 - 3.211)**
Abdominal pain					
No [a]	**97**	**7**	**90**		**1**
Yes	**53**	**4**	**49**	**0.924**	**0.931 (0.215 - 4.039)**

a - reference category.

GABHS in TF, viruses are the most common agents [4]. Viruses have been found to be the causative agent at rates between 42 and 70% in children with acute TF [4, 12,19]. In our study, too, we found that viruses were the most common agent (61%). Moreover, the results suggested additional possible viral agents because in 34% of the patients we did not find any of the viral agents tested. Clinical and laboratory findings in the group where no causative agent was determined had some similarities with the group that tested positive for the viral agents examined here.

A member of the herpes virus family, EBV may cause latent infection by colonization in tonsil tissue [25]. Although EBV infection is usually asymptomatic, it has been associated with mononucleosis in 30 - 50% of adolescents and adults [26]. In another study, in 56% of children with exudative tonsillitis and 75% of those with severe acute exudative tonsillitis were shown to be EBV positive; other viral agents were found in 19% of all patients with exudative tonsillitis [27]. Many studies have reported that the EBV incidence in children after tonsillectomy is 40 - 54% [28-31]. In our study, EBV was the most frequent (50%) of the viral agents detected. EBV-specific ELISA parameters (EBNA IgG/M, VCA IgG/M, and EA-D) need to be assessed to show the status of EBV infection, i.e., acute, past, or latent. In a study of children with acute tonsillitis, adenovirus and HSV were detected in 19% and 2%, respectively. No agent was detected in 35% of cases, and in 14%, more than one viral agent was present [18]. In another study in children with acute pharyngitis, adenoviruses and enteroviruses were found in 10% and 8%, respectively [21]. In the study by McMillan et al., the HSV-1 frequency in children with tonsillopharyngitis was 5.7%, pharyngeal erythema was seen in 71%, and exudate in the pharynx was identified in 40% of the patients. Moreover, 91% of the patients used oral antibiotics. Furthermore, co-occurrence with GABHS was found in



	AUC	Optimum cutoff value	Sensitivity(%)	Specificity(%)
WBC(mm^3)	0.867	15150	100	70
NLR	0.877	6.32	100	74
hsCRP(mg/dL)	0.712	21.60	38	95

Figure 1. ROC curve for WBC, NLR, and CRP values for children with acute tonsillopharyngitis.

2.8% of the patients [13]. In our study, HSV-1 was found in 10.7%, adenovirus in 8.7%, and enterovirus in 5.3% of cases. Although the adenovirus and enterovirus rates in our study were comparable to those in the literature, we found a higher rate of HSV-1. More than one viral agent was identified in 13% of the patients, but no agent was identified in 34%. Moreover, EBV positivity together with GABHS was determined in only 3% of patients. Symptoms and findings such as fever (> 38°C), tonsillar exudates, cervical lymphadenopathy, and abdominal pain are prevalent in GABHS TF [32]. However, no single clinical sign is sufficient to confirm or exclude GABHS TF [33]. Although GABHS TF is usually observed in school-aged children, some studies have found that age is not a good indicator and that GABHS TF can progress with atypical symptoms and findings such as rhinitis, coryza, and low-degree fever, especially in children under the age of 3 years [32,34]. Despite this, there are also studies suggesting that age is a good indicator using the GABHS assay [7,19]. In a study comparing GABHS-positive patients and patients with tonsillitis caused by adenovirus and EBV, although 72% of the adenovirus-positive patients were below the age of 4 years and 70% of EBV-positive patients were below the age of 6, 71% of GABHS-positive patients were above the age of 6; the differences in age between GABHS-positive patients and patients with tonsillitis caused by adenovirus and EBV were significant [35]. Results of another study showed that, whereas 74% of the patients with adenovirus tonsillitis were below the age of 3 years and 71% of the patients with EBV tonsillitis were below the age of 6, 72% of the GABHS-positive patients were older than 6 years [18]. In our study, most of the GABHS-positive patients were aged 5 - 17 years, and viral agent-positive patients were also of the same age. Thus, we found that age was not a good indicator in GABHS diagnosis.

Lin et al. reported that symptoms of throat pain, tonsil-

lar swelling, cervical lymphadenopathy, and scarlatiniform rash were significantly higher in GAS culture-positive patient with pharyngitis. However, even though these findings have strong associations with GABHS, those researchers reported that the sensitivity and specificity were below 50%, so the determination could only help in predicting a probable GABHS infection that required confirmation with a throat culture [6]. Kunnamo et al. compared tonsillitis with GABHS and non-streptococcus tonsillitis in children. They concluded that there were no significant differences in findings of fever, lymphadenopathy, absence of coughing, or absence of nasal flow [20]. It was also reported that fever and tonsillar exudates can usually be seen in TF caused by EBV, adenovirus, and HSV-1 [12,13]. In our study, clinical findings of fever ≥ 38°C, headache, tonsillar exudate, and abdominal pain were not significant in the diagnosis of GABHS. As in many studies, despite the fact that the exudates from the tonsils were not found to be significant predictors of GABHS positivity in our study, this finding continues to be interpreted frequently as indicative of GABHS by clinicians. While EBV, which creates tonsillar exudate, was the most frequently encountered virus in our study, it is not possible to comment on the state of active infection because serological studies regarding EBV were not performed. In the patient group found to be GABHS-positive, the absence of coughing and the presence of painful cervical lymphadenopathy were significantly higher in comparison with the virus-positive group and with those where no agent was detected; however, these symptoms increased the GABHS-positivity risk significantly (Table 3). Although throat culture remains the gold standard in the diagnosis of GABHS, the slow result is an important disadvantage. Early diagnosis and treatment can provide important benefits, such as decreasing symptoms, preventing spread, and decreasing additional examinations [36,37]. Thus, GASRT is used extensively [38]. Maltezou et al. reported that the sensitivity and specificity of GASRT were 83.1% and 93.3%, respectively. However, when used with clinical criteria, the sensitivity changes to 60.9 - 95.8%, and the specificity changes to 86.1 - 96.8% [39]. Tanz et al. found that the sensitivity and specificity of GASRT were 70 and 98%, respectively, in 1848 acute pharyngitis children aged 3 - 18 [40]. Cohen et al. reported a Cochrane analysis that considered 116 studies with 58204 subjects. They found the sensitivity and specificity of GASRT to be 83.3 - 87.6% and 94.5 - 96.2%, respectively. They also reported no difference in sensitivity between enzyme immunoassay (EIA) and optical immunoassay (OIA) tests [22]. Most studies have found specificity to be higher than sensitivity. In our study, the sensitivity and specificity of GASRT were 90% and 97%, respectively, similar to earlier studies in the literature.

Children with TF are diagnosed using the GASRT and throat culture after a clinical assessment, and additional medical examinations may be requested. Kunnama et al. studied GASRT and throat culture; in > 96% of children diagnosed with TF, they also studied CRP in 95% and WBC in 88.5%. However, they found no significant difference in CRP and WBC to separate streptococcal from non-streptococcal tonsillitis [20].

Putto et al. also found no significant difference in WBC, CRP, or sedimentation values in trying to differentiate between viral and bacterial agents in two studies [18, 19]. Sun et al. studied tonsillitis with GABHS, adenovirus, and EBV and found no significant difference in CRP, WBC, or sedimentation values among the patients [35]. In our study population, WBC, NLR, and CRP were significantly higher in GABHS-positive patients compared with the virus-positive group and the group where no agent was detected (Table 2). The sensitivity of WBC and NLR were higher in diagnosing GABHS using the optimum cutoff values, 15150/mm^3 for WBC and 6.32 for NLR; specificity of CRP was high using the optimum cutoff value for CRP, 21.6 mg/dL. The sensitivity and specificity of ASO and sedimentation values were low in diagnosing GABHS. Furthermore, increases in acute-phase reactants can be seen in many other systemic bacterial infections apart from GABHS. For this reason, an increase in only acute-phase reactants is not a specific indicator for the diagnosis of GABHS. The fact that we investigated only four viral TF agents is a limitation of our study. Additionally, we could not assess active versus latent infection by the most frequent viral agent in our study (EBV) because of a lack of serological data.

CONCLUSION

The data presented here show clearly that the causative agent of acute TF in children is usually a virus. Even when typical clinical findings were not present, EBV was the most common viral agent in TF. According to epidemiological data, age is not a good indicator of tonsillitis based on the GABHS assay. It can be concluded from the clinical findings that the absence of coughing and the presence of painful cervical lymphadenopathy can be important indicators in the diagnosis of GABHS positivity. Furthermore, GASRT is an assay that is fast, readily applicable, and inexpensive. Moreover, WBC, NLR, and CRP were significantly higher in GABHS-positive patients.

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