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Investigation of the Prevalence of Group A Beta-haemolytic *Streptococcus* and Efficiency of *Streptococcus* Rapid Antigen Test in Patients Prediagnosed with Acute Tonsillopharyngitis in a University Hospital

Bir Üniversite Hastanesinde Akut Tonsillofarenjit Ön Tanısı Almış Hastalarda A Grubu Beta-hemolitik Streptokok Sıklığının ve Streptokok Hızlı Antijen Testi Etkinliğinin Araştırılması

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Abstract

Introduction: Acute tonsillopharyngitis is the most important infectious cause of hospital admission in pediatric age groups. The aim of this study was to investigate the prevalence of group A beta-hemolytic streptococci in patients prediagnosed with acute tonsillopharyngitis in a university hospital in Northern Cyprus and determine the effectiveness of *Streptococcus* rapid antigen test (SRAT) in diagnosis.

Materials and Methods: Patients with acute tonsillopharyngitis prediagnosis and admitted to our hospital between September 1, 2015 and December 31, 2017 were retrospectively screened from physical and electronic records. Patients with a throat culture and/or SRAT result were included in the study. Culture method was used as the golden standard. Statistical analysis was performed with SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) programme and $p<0.05$ was considered statistically significant.

Results: The study group included 1,023 patients with acute tonsillopharyngitis prediagnosis and throat culture test. For 508 (49.7%) of patients, both culture and SRAT results were reported. Mean age was 14.5 years (age range 0-89) and there were 506 (49.5%) females and 517 (50.5%) males. Prevalence of disease was detected to be 22.8% in the 5-15 age group and 14.9% in all age groups. Positivity of both SRAT and throat culture tests was statistically significant in the 5-15 age range ($p<0.001$, $p<0.001$ respectively). SRAT had a sensitivity of 58% and a specificity of 91%. Positive predictive value and negative predictive value were detected as 54% and 93%, respectively.

Conclusion: Our study results represent the first dataset investigating streptococcal tonsillophayngitis and SRAT efficiency in Northern Cyprus. Despite its relatively low sensitivity, due to the high specificity of SRAT, we conclude that it will be beneficial for clinicians in prompt diagnosis and treatment, and will prevent inappropriate antibiotic use.

Keywords: *Streprococcus* pyogenes, tonsillitis, prevalence, epidemiology, upper respiratory tract infection

Öz

Giriş: Akut tonsillofarenjit, özellikle çocuk yaş gruplarında hastaneye başvuru nedenlerinin en önemli enfektif nedeni kabul edilmektedir. Bu çalışmada, Kuzey Kıbrıs'taki bir üniversite hastanesinde akut tonsillofarenjit ön tanısı almış hastalarda A grubu beta-hemolitik streptokok sıklığının araştırılması ve streptokok hızlı antijen saptama testinin (SHAT) tanıdaki etkinliğinin belirlenmesi amaçlanmıştır.

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Öz

Gereç ve Yöntem: Hastanemize 01.09.2015-31.12.2017 tarihleri arasında başvuran ve akut tonsillofarenjit ön tanısı alan hastalar restrospektif olarak fiziki ve elektronik hasta kayıtlarından tarandı. Boğaz kültürü ve/veya streptokok hızlı antijen testi yapılan hastalar çalışmaya dahil edildi. Verilerin değerlendirilmesinde kültür yöntemi altın standart test olarak kabul edildi. Verilerin istatistiksel analizi için SPSS Ver. 13.0 (SPSS Inc., Chicago, IL, ABD) programı kullanıldı ve p<0,05 anlamlı kabul edildi.
Bulgular: Çalışma grubunda bulunan akut tonsillofarenjit ön tanılı ve boğaz kültürü olan 1,023 hasta çalışmaya alındı. Bu hastaların 508'inin (%49,7) hem boğaz kültürü hem de SHAT sonuçları vardı. Yaş ortalaması 14,5 (0-89 arasında) olup, bunların 506'sı (%49,5) kadın ve 517'si (%50,5) erkekti. Hastalığın prevalansı tüm yaş gruplarında %14,9, 5-15 yaş grubunda ise %22,8 olarak tespit edilmiştir. Boğaz kültürü ve SHAT'de saptanan pozitiflik oranları 5-15 yaş grubunda istatistiksel olarak anlamlı derecede yüksek saptanmıştır (sırasıyla p=0,001, p=0,001). SHAT duyarlılığı %58, özgüllüğü %91, pozitif prediktif değeri %54 ve negatif prediktif değeri %93 idi.
Sonuç: Streptokokal tonsillofarenjit sıklığı ve SHAT testinin etkinliğini değerlendirdiğimiz çalışmamızın sonuçları, Kuzey Kıbrıs Türk Cumhuriyeti için ilk verileri oluşturmaktadır. SHAT testinin duyarlılığı nispeten düşük olsa da özgüllüğünün yüksek olması nedeni ile klinisyenlere hızlı tanı ve tedavi olanağı sağlayacağı ve uygunsuz antibiyotik kullanımını azaltacağı kanısındayız.
Anahtar Kelimeler: *Streptococcus* pyogenes, tonsillit, prevalans, epidemiyoloji, üst solunum yolu enfeksiyonu

Introduction

Tonsillopharyngitis is among the most common causes of presentation to healthcare centers. Although it is most commonly seen between the ages of 5 and 15 years, it can affect all age groups[1,2]. While many microorganisms can cause tonsillopharyngitis, viruses are usually implicated in its etiology. Among bacterial infections, group A beta-hemolytic streptococci (GABHS) are the most common causative agents[3-5].

Acute rheumatic fever (ARF) is a complication associated with streptococcal tonsillopharyngitis and is an important cause of morbidity and mortality. Therefore, differentiating between viral and bacterial tonsillopharyngitis infections as early as possible is a key clinical step[4,6,7]. In the past 20 years, rapid immunochromatographic tests based on the presence of polysaccharide C antigen in the bacterial cell wall have been developed for the detection of GABHS. The time from obtaining a swab sample to obtaining culture results is relatively long (24-48 hours), causing delayed treatment or unnecessary antibiotic use. The shorter turnaround time of rapid antigen tests enables early antibiotic treatment, which shortens disease duration, reduces contagiousness, and prevents complications[4,8]. Some other *Streptococcus* species found in the normal throat flora may lead to false positive results because they carry the same carbohydrate antigens as GABHS. On the other hand, it is considered an advantage that negative results from the *Streptococcus* rapid antigen test (SRAT) in most patients prevent unnecessary antibiotics use[9,10].

The aim of this study was to determine the effectiveness of the SRAT used in addition to throat culture, which is regarded as the gold standard for the diagnosis of streptococcal tonsillopharyngitis, and to investigate the false-negative and false-positive rates of this test. Our other objectives were to determine the prevalence of GABHS among patients with prediagnosis of acute tonsillopharyngitis in our center and to contribute to the literature by presenting the first study on this subject from Northern Cyprus.

Materials and Methods

The study included patients who underwent throat culture and/or rapid antigen test for suspected acute tonsillopharyngitis in our center between September 1, 2015 and December 12, 2017. Importantly, some of the patients had two swabs and some of them had one swab. Patients' exact clinical data were not recorded.

Samples sent to our microbiology laboratory were inoculated into appropriate medium according to the throat culture protocol[2]. The cultures were evaluated for beta-hemolytic colony presence after 24-48 hours of incubation at 35 °C. SRAT was performed using the commercially available immunochromatographic BioNexia Strep A plus (bioMérieux, Craponne, France) test in accordance with the manufacturer's recommendations.

Statistical Analysis

SPSS version 13.0 (SPSS Inc., Chicago, IL) software was used for statistical analysis of the data. Pearson's chi-square test was used to evaluate the positivity rates of throat culture and SRAT among the age groups (<5, 5-15, and >15 years). P<0.05 was considered statistically significant. SRAT sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, as well as disease prevalence and false-negative and false-positive rates[11]. As this study was retrospective and based mainly on laboratory data, ethics committee approval was not received.

Results

Of the 1,023 patients included in the study, 508 (49.7%) underwent both throat culture and rapid antigen test, while 515 (50.3%) had throat culture only (Table 1). Patient

age ranged between 0 and 89 years and the mean age was 14.5±19.2 years. The study group included 506 female patients (49.5%) and 517 male patients (50.5%). The results of patients with both throat culture and SRAT are summarized in Table 1.

According to the data obtained in this admission-based study, the prevalence of GABHS in patients with prediagnosis of acute tonsillopharyngitis was 14.9% (152/1,023 patients). The SRAT was found to have 58% sensitivity and 91% specificity in diagnosing the disease. In light of the data in Table 1, PPV was 54% and NPV was 93%. Finally, the false-positive rate was 9% and false-negative rate was 42%.

When the throat culture and SRAT results of the patients in the study group were evaluated in terms of gender (Table 1), there was no statistically significant difference (p=0.974, p=0.507, respectively).

When throat culture and SRAT results were evaluated according to age, positivity rates were highest for both tests between the ages of 5 and 15 years, and the difference was statistically significant (Table 2) (Figure 1).

Discussion

Although most cases of acute tonsillopharyngitis are viral, GABHS are responsible for bacterial infections in 15-30% of pediatric cases and 5-10% of adult cases[10]. Streptococcal tonsillopharyngitis is the most common disease among school-age children. Its prevalence is especially high in the 5-15 year age group. ARF is the most important known complication of the disease. ARF is uncommon in children under the age of 4 and is especially rare under the age of 2 years[12]. Therefore, it is important to know its prevalence in the community and control it with appropriate antibiotics.

The prevalence of streptococcal tonsillopharyngitis varies from country to country. In a study by Sayğılı et al.[4] including 1,934 patients in Turkey, the prevalence of GABHS was 11% overall and 14.4% in children aged 5-15 years. In another study conducted among patients in Turkey aged 0-18 years, the prevalence was 25%[3]. A study in Erzurum, Turkey to determine the incidence of GABHS in patients with upper respiratory tract infection (URTI), revealed a lower prevalence (6.51%) compared to similar studies conducted in Turkey[13]. In a meta-analysis by Oliver et al.[14], the average prevalence of GABHS in the 5-19 year age group in countries with high socioeconomic status was found to be 36.8%. However, the average prevalence in 188 different studies encompassing all age groups was reported as 25.2%. In another meta-analysis by Barth et al.[15] reviewing studies conducted on the African continent, the prevalence of GABHS was 21% (range 17-26%) among patients (aged 2 months-92 years) diagnosed with pharyngitis in 25 studies. In the same study, rates for the <18 and >18 year age groups were 22% and 21%, respectively. According to the data obtained from our study,

Table 1. Distribution of *Streptococcus* A rapid antigen test for and throat culture results

	SRAT positive	SRAT negative	Total
Throat culture positive	44 (8.7%)	32 (6.3%)	76 (15%)
Male	27 (10%)	15 (5.5%)	42 (15.5%)
Female	17 (7.2%)	17 (7.2%)	34 (14.4%)
Throat culture normal flora	38 (7.5%)	394 (77.5%)	432 (85%)
Male	14 (5.2%)	215 (79.3%)	229 (84.5%)
Female	24 (10.1%)	179 (75.5%)	203 (85.6%)
Total	82 (16.2%)	426 (83.8%)	508 (100%)
Male	41 (15.2%)	230 (84.8%)	271 (100%)
Female	41 (17.3%)	196 (82.7%)	237 (100%)

SRAT: *Streptococcus* rapid antigen test

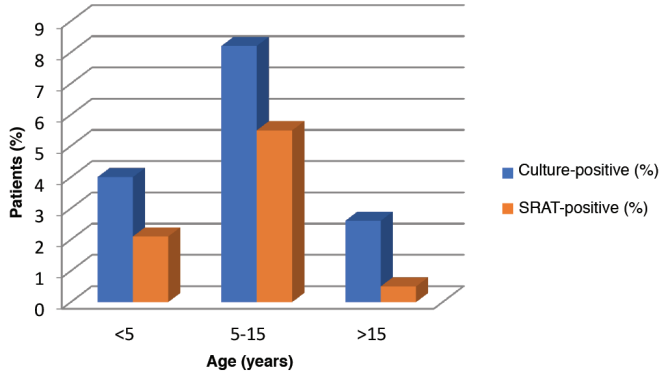

Figure 1. Distribution of patients with positive *Streptococcus* A rapid antigen test (SRAT) and throat culture results by age group

SRAT: Streptococcus rapid antigen test

Table 2. Distribution of *Streptococcus* A rapid antigen test for and throat culture results by age group

Age (years)	<5	5-15	>15	Total	p
Culture total	392 (38.3%)	368 (36%)	263 (25.7%)	1023 (100%)	0.001
Culture positive	41 (26.9%)	84 (55.3%)	27 (17.8%)	152 (100%)	
SRAT total	242 (47.6%)	223 (43.9%)	43 (8.5%)	508 (100%)	0.001
SRAT positive	21 (25.6%)	56 (68.3%)	5 (6.1%)	82 (100%)	

SRAT: *Streptococcus* rapid antigen test

the prevalence of the disease was found to be 14.9% in all age groups and 22.8% in the 5-15 year age group. In addition, the prevalence rates of our study constitute the first literature data for the Turkish Republic of Northern Cyprus. The prevalence of streptococcal tonsillopharyngitis was consistent with many other studies, especially those focused on Turkey.

Viruses are the causative agents in most cases of acute tonsillopharyngitis. Only 15-30% of cases are caused by GABHS and require antibiotic therapy. It is very difficult to diagnose URTIs caused by GABHS based on the patient's history and clinical symptoms, even for experienced physicians[10,13,16]. Throat culture is accepted as the golden standard for the diagnosis of GABHS infection. When samples are taken from the right person, from the right site, with the right technique and are cultured under the appropriate conditions, throat culture has high sensitivity and specificity[4]. However, the time from throat swab collection to receiving the culture result is long (24-48 hours), causing treatment delays or unnecessary antibiotic use. The SRAT provides the results much more quickly and enables early antibiotic treatment, which shortens disease duration, reduces contagiousness, and prevents complications[4,8]. There are more than 40 different commercially available SRATs used to detect GABHS. Their sensitivity ranges between 70% and 90%, while their specificity is over 95%. The manufacturer of the BioNexia Strep A plus test used in our study reported its sensitivity as 94% (88-98%) and its specificity as 98% (96-99%)[17]. In a study by Sayğılı et al.[4] including 1,934 patients aged 1-75 years, the sensitivity and specificity of the BioNexia rapid antigen test compared with bacterial culture was found to be 84.1% and 100%, respectively. According to the results of five different studies conducted in Turkey, SRAT sensitivity and specificity were 64.6-68.2% and 89.7-99%, respectively[2]. In another study focused on Turkey, a different kit was used and the SRAT was found to have a sensitivity of 68.1% and specificity of 92.2%[2]. In a study of two different pediatric groups, one including 639 subjects aged 0-6 years and the other including 253 subjects aged 7-17 years, the sensitivity and specificity of the SRAT were reported to be 59.5% and 97.2%, respectively[18]. These values were compatible with data in our study (58% sensitivity and 91% specificity). One of the major factors affecting the sensitivity and specificity of an SRAT is the amount of inoculum transferred from the swab. Other factors include the use of different laboratory kits, the skill of the tester, the prevalence of GABHS in the region, and the sampling technique[4,18]. We believe that the above mentioned factors affected the sensitivity and specificity of the Strep A test performed at our hospital.

Another problem with SRATs is that they may yield false negative or false positive results. A meta-analysis of a total of 19 different studies and 8,136 subjects (between 1996 and 2010) determined the false negative rate of SRATs to be 15.5% (5.3-27.6%)[6]. In our study, the false negative rate was 42%. In the literature, the most important factor in obtaining a false negative result for a SRAT is mentioned to be the amount of streptococci present in the throat swab and the method used[19]. The high false-negative results observed in our study may be due to the fact that only a single throat swab sample could be obtained from some of our patients, and the bacterial amount was further reduced since SRAT was performed after throat culture. Our clinician notified the relevant departments to eliminate such problems with throat swabs. Confirming a negative SRAT result with culture is important to prevent misdiagnosis and inadequate treatment and thereby avoid important complications such as ARF[3,4,16].

False positive results from SRATs have been attributed to non-GABHS species found in the normal throat flora (*Streptococcus milleri, Streptococcus intermedius*) that carry the same carbohydrate antigens as GABHS[3,20]. In a large meta-analysis, the mean false-positive rate in 19 different studies on the SRAT was 8.7% (0-37.5%)[6]. Çoban et al.[2] reported no SRAT false positives in their study conducted in Antalya, Turkey, while Gözüküçük et al.[3] reported a false positive result for only 1 patient (1%) in their study. In another study, the false-positive rate was found to be 2.1%[15]. Hence, the false-positive rate of SRAT in our study was 9%, which we concluded was probably due to non-GABHS species that may be present in the normal throat flora.

The main limitations of our study were the collection of single or double swab samples from some of the cases and lack of patients' symptomatic information.

Conclusion

In the present study, which to the best of our knowledge is the first study in Northern Cyprus to investigate the prevalence of group A *Streptococcus* in patients with suspected tonsillopharyngitis, this prevalence was 14.9% for all age groups and 22.8% for the 5-15 year age group.

Although our SRAT resulted in a relatively low sensitivity compared to the literature, these tests facilitate early diagnosis and appropriate treatment. Patients with negative results will not use antibiotics unnecessarily, thereby pcontributing to the decreament of bacterial resistance.We also conclude that the negative SRAT results of children aged 5-15 years should be confirmed with throat culture considering the high false-negative rate. This may help prevent misdiagnosis and inadequate treatment. It is also apparent that collecting two different swab samples for the two tests (culture and SRAT) will strengthen the diagnosis. In conclusion, we believe that the rapid antigen test is a quick and reliable test that assists clinicians in the diagnosis of streptococcal tonsillopharyngitis.

Ethics

Ethics Committee Approval: As this study was retrospective and based mainly on laboratory data, ethics committee approval was not received.

Informed Consent: Since this was a retrospective study informed consent was not received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., K.S., C.D., Concept: E.G., K.S., C.D., Design: M.G., B.B., Data Collection or Processing: C.D., K.S., Analysis or Interpretation: E.G., Literature Search: E.G., M.G., Writing: E.G., B.B.

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