

Variation in Clinical Presentation of Childhood Group A Streptococcal Pharyngitis in Four Countries

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Summary

We conducted a cross-sectional study from September 2001 to August 2003 during which children between 2 and 12 years of age presenting with complaint of sore throat were recruited from urban pediatric clinics in Brazil, Croatia, Egypt and Latvia. The objective of the study was to compare clinical signs and symptoms of children presenting to urban pediatric clinics with sore throat in and between countries and to identify common clinical criteria predicting group A beta hemolytic streptococcal (GAS) pharyngitis. Using a single standard protocol in all four sites, clinical data were recorded and throat swabs obtained for standard GAS culture in 2040 children. Signs and symptoms were tested for statistical association with GAS positive/negative pharyngitis, and were compared using χ^2 tests, ANOVA and Odds Ratios. Clinical signs of GAS pharyngitis in children presenting to clinics varied significantly between countries, and there were few signs or symptom that could statistically be associated with GAS pharyngitis in all four countries, though several were useful in two or three countries. Our results indicate that the clinical manifestations of pharyngitis in clinics may vary by region. It is therefore critical that clinical decision rules for management of pharyngitis should have local validation.

Key words: clinical signs, streptococcal pharyngitis, Group A beta hemolytic streptococcal (GAS).

Introduction

Untreated group A beta hemolytic streptococcal (GAS) pharyngitis is the precipitating cause of rheumatic fever and subsequent rheumatic heart disease, the most common cause of acquired heart disease in children and adults worldwide [1, 2]. Despite having largely disappeared in high-income

countries, rheumatic heart disease continues to be a significant public health problem in low-income countries, causing an estimated 400 000 deaths annually, mostly among children and young adults [1, 3–5]. Current understanding of the epidemiology and clinical features of GAS pharyngitis is largely derived from studies conducted in high-income (mostly Northern or temperate climate) countries where rheumatic fever and rheumatic heart disease are rare. In low-income countries, where rheumatic fever and rheumatic heart disease continue to pose significant public health problems, there are few indexed prospective studies documenting the epidemiology and clinical presentation of GAS pharyngitis.

Throat culture is the internationally accepted gold standard for the diagnosis [6]. However, in low-income countries where financial resources limit the widespread use of laboratory tests for GAS diagnosis, accurate clinical criteria are needed for the

Acknowledgements

This study was supported by USAID. The Croatian and Latvian site was funded by the Department of Child and Adolescent Health and Development, World Health Organization, Geneva.

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management of GAS pharyngitis. Earlier studies have indicated that signs and symptoms of GAS pharyngitis are often indistinguishable from those observed in non-GAS pharyngitis [7, 8].

We initiated a prospective descriptive study to define the variation in clinical presentation of GAS pharyngitis within and between four countries to determine if there is a group of common signs and/or symptoms that could be used to accurately predict GAS pharyngitis in children residing in geographically and culturally distinct regions.

Methods

Children were enrolled in four urban university pediatric outpatient clinics from September 2001 to August 2003 in Rio de Janeiro, Brazil; Cairo, Egypt; Riga, Latvia and Zagreb, Croatia. Children between 2 and 12 years of age presenting to participating outpatient clinics were screened for enrollment if he/she presented with one or more of the following complaints: cough, cold and/or sore throat. Exclusion criteria included reports of one or more of the following: oral antibiotic use within 3 days preceding or intramuscularly administered antibiotics within 28 days prior to the clinic visit; a history of previous rheumatic fever or rheumatic heart disease; or hospitalization for any reason.

All study sites used a common study protocol, standard methods for biological specimen collection and laboratory analysis, and standard data collection forms translated into the local language [9]. The study protocol was approved by local and national ethical review boards at each participating clinical site, the World Health Organization in Geneva and the Johns Hopkins Bloomberg School of Public Health. Informed consent was obtained from the parent or guardian accompanying the child to the clinic and child assent was obtained from all participating children aged 5 years and older.

After enrollment, demographic data were recorded and a physical examination was performed by a pediatrician. In all sites, throat cultures were obtained and plated onto 5% sheep blood agar plates, incubated at 37°C and examined at 24 and 48 h for the presence of beta-hemolytic streptococci and confirmed by bacitracin disc [10].

In all sites, we conducted a standardization exercise with participating clinicians to minimize inter-rater variation in the identification of signs and symptoms. The exercise consisted of a series of clinical photographs of pharynges, which were shown on a projection screen. Physicians were asked to mark forms containing a list of collected signs associated with streptococcal pharyngitis. Participants were asked to mark each sign as either absent, present, not applicable or unknown for each clinical photograph. A discussion followed the viewing and

assessment of signs, to clarify the characteristics and severity of signs displayed in each photograph.

Statistical analysis

For the purpose of this analysis, we included only children who presented with complaint of sore throat. Demographic data was recorded for each patient and compared with throat culture results. Patients were categorized into either GAS positive or GAS negative based on laboratory results of throat swabs. Signs and symptoms among groups were compared using χ^2 for proportions (adjusted for multi-group comparisons) and ANOVA for comparison of means. All analyses were conducted using the statistical software STATA 9.0 [11].

Results

Patient characteristics

A total of 2040 children with complaint of sore throat were enrolled at participating clinics. Demographic characteristics of these enrolled children varied significantly by country. The proportion of children with a positive GAS culture was 29.2% overall, ranging from 26.8% in Brazil to 42.0% in Croatia ($p < 0.001$). The mean age of patients for all sites was 5.3 (± 2.6) years but means varied among sites from 4.9 (± 0.06) in Egypt to 6.6 (± 0.38) in Latvia ($p < 0.001$). The proportion of children below the age of 5 was 41.7%, and varied among countries from 31.5% in Latvia to 67.2% in Egypt ($p < 0.001$). Female patients comprised 43.1% of the study population, ranging from 42.0% in Croatia to 50.6% in Brazil ($p = 0.197$) (Table 1).

Clinical characteristics of GAS pharyngitis

Table 2 and Fig. 1 display the prevalence of signs and symptoms commonly associated with streptococcal pharyngitis in children enrolled in each country. Clinical presentation of GAS pharyngitis varied significantly between countries, and there were no signs or symptoms that could statistically discriminate between patients with GAS and non-GAS pharyngitis across all four countries. The age group with the highest frequency of GAS pharyngitis was 5–9 years for all sites except Latvia, where it was 10–12 years of age. In Brazil, patients ≥ 5 years of age were statistically more likely to be GAS+ than those < 5 years ($p < 0.001$) though in Egypt and Latvia, patients < 5 years of age were more likely to be GAS+ than those ≥ 5 years of age ($p < 0.005$ and $p < 0.001$, respectively). In Croatia there were no statistically significant differences in incidence of GAS pharyngitis between age groups. The peak season for GAS pharyngitis varied by site. In Brazil, which is in the southern hemisphere, fall and winter were equally associated with GAS pharyngitis (March–August). In Egypt and Croatia, the majority

TABLE 1
Comparison of selected patient characteristics by site

Site	Patient characteristics			
	GAS+ n (%)	% Female n (%)	Age <5 years n (%)	Mean age (Years ± SD)
Brazil (n = 170)	44 (26.8)	86 (50.6)	90 (42.4)	5.5 ± 0.2
Croatia (n = 200)	84 (42.0)	84 (42.0)	86 (32.0)	6.4 ± 0.1
Egypt (n = 1410)	384 (27.3)	594 (43.1)	947 (52.8)	4.9 ± 0.1
Latvia (n = 260)	77 (29.4)	119 (45.7)	81 (31.2)	6.6 ± 0.4
P-value (χ^2 or t-test)	<0.001	0.106	<0.001	0.001

TABLE 2
Signs and symptoms of GAS pharyngitis by country

Country n (%) GAS+	Brazil 45 (28.8%)			Croatia 84 (42.0%)			Egypt 385 (27.3%)			Latvia 77 (29.3%)		
	n (%)	OR	p	n (%)	OR	p	n (%)	OR	p	n (%)	OR	p
Fever	41 (91)	1.45	0.530	55 (67)	0.97	0.932	324 (84)	1.19	0.292	67 (88)	0.959	0.922
Chills	18 (40)	1.57	0.212	30 (36)	0.94	0.844	151 (39)	1.30	0.034	53 (69)	1.06	0.842
Rhinitis	14 (31)	0.49	0.054	39 (46)	0.75	0.328	171 (44)	0.66	0.001	26 (34.2)	0.89	0.675
Congestion	15 (33)	0.59	0.150	35 (42)	0.58	0.060	134 (35)	1.10	0.451	42 (55)	1.02	0.956
Difficulty swallowing	39 (87)	4.58	0.001	63 (75)	2.52	0.003	346 (90)	1.51	0.031	51 (67)	1.91	0.025
Cough	15 (33)	2.11	0.073	25 (30)	2.03	0.020	224 (58)	1.36	0.029	25 (33)	1.48	0.254
Vomiting	8 (18)	0.75	0.525	21 (25)	0.71	0.290	94 (24)	1.13	0.387	20 (26)	1.17	0.614
Hoarseness	14 (31)	1.31	0.480	31 (37)	1.07	0.821	100 (26)	1.29	0.068	32 (43)	3.28	<0.001
Cervical adenopathy	26 (58)	5.53	<0.001	46 (55)	2.06	0.013	88 (23)	1.49	0.007	59 (78)	1.56	0.164
Palatal petechiae	6 (13)	1.40	0.531	25 (30)	3.36	0.001	3 (1)	1.60	0.520	22 (29)	3.00	0.001
Strawberry tongue	45 (100)	—	—	18 (21)	2.60	0.021	8 (2)	1.67	0.266	26 (34)	1.64	0.095
Pharyngeal erythema	44 (90)	1.43	0.500	84 (100)	—	—	383 (100)	2.65	0.198	76 (98)	0.83	0.880
Enlarged tonsils	36 (74)	4.21	<0.001	84 (100)	—	—	290 (75)	1.19	0.211	63 (81)	1.37	0.356
Pharyngeal/tonsillar exudate	24 (49)	3.51	0.001	40 (48)	1.24	0.450	114 (30)	1.44	0.007	7 (9)	0.92	0.863

Highlighted box indicates statistically significant association ($p < 0.05$) with GAS+ throat culture.

Sign / Symptom	Brazil	Croatia	Egypt	Latvia
Fever				
Chills			X	
Rhinitis			X	
Congestion				
Difficulty swallowing		X	X	X
Absence of cough			X	
Vomiting				
Hoarseness				X
Cervical adenopathy	X	X	X	
Palatal petechiae		X		X
Strawberry tongue		X		
Erythema				
Enlarged tonsils	X			
Exudate	X		X	

FIG. 1. Signs/symptoms associated with GAS pharyngitis by country.

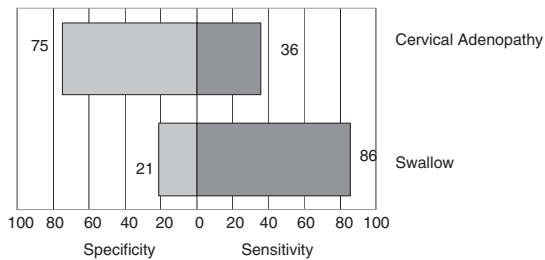


FIG. 2. Range of sensitivity and specificity of cervical adenopathy and pain on swallowing, by site.

of GAS pharyngitis cases occurred in the autumn months between September and November. In Latvia, the majority of cases of GAS pharyngitis were observed in the winter, between December and February. In Brazil, the majority of GAS pharyngitis cases occurred in winter and spring months, which in the southern hemisphere occurred between April and August. Fig. 2 displays the variation in the sensitivity and specificity of the most common sign and symptom in all four countries, showing the fairly wide variation of these indices.

Discussion

In this study, the clinical presentation and rates of GAS pharyngitis varied significantly by site. In our study, the local fall and winter months were consistently the peak times for GAS pharyngitis across all sites, which differ from what has been previously reported in studies in temperate and tropical regions. In temperate regions of the world, it has been reported that the GAS incidence peaks during the winter/spring months [12, 13]. In tropical regions the peak incidence of GAS and non-GAS pharyngitis is in March and April [14, 15].

Although the presenting signs and symptoms of pharyngitis varied by site and by GAS status, of particular interest was that some of the clinical features of GAS pharyngitis in children widely cited in textbooks, namely fever, pharyngeal erythema, cervical adenopathy and palatal petechiae [8, 16] did not usefully discriminate between GAS and non-GAS pharyngitis in all participating study sites. This finding has been observed in previous studies [17–19]. The only symptom that was statistically associated with GAS pharyngitis in all four sites was difficulty in swallowing. The sign of cervical adenopathy was significantly associated with GAS pharyngitis in three of the four countries: Brazil, Croatia and Egypt, but not in Latvia. Absence of cough was positively associated with GAS pharyngitis in Croatia and Egypt; pharyngeal and/or tonsillar exudate was positively associated with GAS pharyngitis in Brazil and Egypt; and palatal petechiae

were positively associated with GAS pharyngitis in Croatia and Latvia.

Differences in clinical epidemiology of GAS pharyngitis have been shown by others to vary by geography and climate [20]. Because our study included four countries with diverse geography and climate we are not able to consider the possibility that there may be similarities in the clinical presentation and/or epidemiology of GAS in countries within the same region or with similar epidemiologic profiles. This may be related to circulation of GAS strains and the immunity profile of the various populations [21].

Our study had certain limitations. There were differences in sample size in each study site. Egypt had a significantly greater number of patients enrolled than other sites due to the size of the participating clinic and volume of patients who were eligible and agreed to participate in the study. Additionally, since the study was conducted in four distinct study sites there may have been variations in the identification of signs and symptoms by participating study physicians. We used a common protocol, a common training manual and a standardization exercise in all four sites to control for this variation in physician identification to the best of our ability. Similarly, there may have also been differences in laboratory diagnosis of GAS. We also used a common protocol, standardized training and made supervisory visits to all participating sites to ensure standard laboratory methods. Finally, variation in clinical presentation of GAS and non-GAS pharyngitis between countries may have been attributable to site specific differences in patient recruitment and screening practices, number of carriers with inter-current viral infections, populations served by participating health facilities, local population access to care, care-seeking behavior and cultural perceptions of sore throat.

Conclusions

In the United States and some industrialized countries it is generally recommended that streptococcal pharyngitis should be confirmed by laboratory testing before antibiotic treatment if needed. However, laboratory testing is not feasible or available in low resource regions of the world and clinicians rely on clinical diagnosis to determine whether or not to treat suspected GAS pharyngitis [8, 9, 22–24]. Our results indicate that clinical signs and symptoms associated with GAS pharyngitis vary substantially by region, which suggests that developing a single sensitive and specific clinical prediction rule for all regions of the world would be a challenge [25]. Although some may feel it is impractical to suggest that individual countries conduct national and/or sub-national studies to determine the most common local signs and symptoms of GAS, there is a need for regional clinical data to determine valid indicators for locally useful clinical prediction rules, validated

decision rules are available for North America [9, 23, 24, 26]. This is particularly important in regions where rheumatic fever and rheumatic heart disease remain diseases of major public health significance.

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