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Research Article

Streptococcus pyogene and its Immunologic Disorders in an Endemic Era: A Review: Article in Iran

Samileh Noorbakhsh[1]* and Farideh Ebrahimi Taj[2]

[1]Full Professor in Pediatric Infectious Disease, Research Center of Pediatric Infectious Diseases, Iran University of Medical Sciences, Iran
[2]Assistant Professor in Pediatrics, Research Center of Pediatric Infectious Diseases, Iran University of Medical Sciences, Iran

***Corresponding Author**: Samileh Noorbakhsh, Research Center of Pediatric Infectious Diseases, 4th floor Hazrat Rasul Hospital, Niayesh Street, Satarkhan Avenue, Tehran, Islamic, Iran.

Received: February 15, 2017; **Published:** March 09, 2017

Abstract

Introduction: It is estimated that between 5 - 15% of normal individuals harbor Group A ß-hemolytic Streptococcus (GABHS) usually in the respiratory tract, without signs of disease. GABHS disorders and its side effects are the major concern specially in pediatric populations. The prevalence of GABHS and delayed immunologic side effects and also antibiotic susceptibility among young population in different parts of Iran is so important.

Material and Methods: Twenty five 25 indexed studies (laboratory or medical reports) about GAS in Iranian population (English or Persian with English abstract) between 2000 - 2015 reviewed.

Conclusion: The carrier state for GABHS in Iranian children are much lower (3 - 6%) than its rate in children living in developed countries but recently a high rate of Group G streptococci were reported in Iran Frequent antibiotic treatment in Iran; exposure at different ages and different seasonality could be the reasons for this wide differences. Rapid immunological GABHS antigen test in compare with conventional throat cultures, showed higher advantage for diagnosis especially in the cases with previous antibiotic usage.

Keywords: *GABHS; OCD; PANDAS; ARF; APSGN*

Abbreviation

GABHS: Group A Beta Hemolytic Streptococcus; OCD: Obsessive-Compulsive Disorder; PANDAS: Pediatric Autoimmune Psychiatric Disorders; ARF: Acute Rheumatic Fever; APSGN: Acute Post Streptococcal Glomerulonephritis

Introduction

Group A beta hemolytic streptococcus (GABHS) is a Gram-positive, non-motile, non-spore forming coccus that occurs in chains or in pairs of cells. The metabolism of *S. pyogenes* is fermentative; the organism is a catalase-negative, facultative anaerobe which requires blood to grow. GABHS have a capsule composed of hyaluronic acid and exhibit beta hemolysis on blood agar. GABHS produces some virulence factors and potentially induces wide spectrum of diseases. Virulence factors of GABHS include: (1) M protein, cell-associated protein (Protein F) and lipoteichoic acid for adherence; (2) hyaluronic acid capsule as an immunological disguise and to inhibit phagocytosis; M-protein to inhibit phagocytosis invasins such as streptokinase, streptodornase (DNase B), hyaluronidase, and streptolysins; exotoxins, such as pyrogenic (erythrogenic) toxin which causes the rash of scarlet fever and systemic toxic shock syndrome [1,2].

Epidemiology: GABHS is one of the most frequent pathogens in human infective diseases. It is estimated that between 5 - 15% of normal individuals harbour GABHS, usually in the respiratory tract, without signs of disease. When the host defense is compromised, or when the organism is able to exert its virulence, or when it is introduced to vulnerable tissues or hosts, an acute infection occurs. Acute GABS infections may present as pharyngitis, scarlet fever (rash), impetigo (infection of the superficial layers of the skin) or cellulitis (infection of

the deep layers of the skin). Toxicogenic infections ususally diagnosed as necrotizing fasciitis, myositis and streptococcal toxic shock syndrome. Delayed immune mediated sequelae of GABS includes post streptococcal glomerulonephritis and acute rheumatic fever. Recently, an unexplained increase in variety, severity and sequelae of GABHS infections, reported. The reasons for resurgence of severe invasive GABHS infections, prompting descriptions of "flesh eating bacteria" in the news media are not completely explained. Today, the pathogen is a major concern because of the occasional cases of rapidly progressive disease and because of the small risk of serious sequelae in untreated infections. These diseases remain a major worldwide health concern, and effort is being directed toward clarifying the risk and mechanisms of these sequelae and identifying rheumatogenic and nephritogenic strains of GABHS [1,2].

URT Infection is common in Iranian children [3,4] and pharyngitis is a common disease in Iranian populations [5]. First, Gharagozloo., *et al.* (1974) isolated GABHS in 26% of 578 patients with URTI; 74% were considered as viral [6]. Gharagozloo., *et al.* (1974) also investigated the prevalence of GABHS,ARF and rheumatic heart disease in certain communities in Tehran, which results are unavailable on line [7]. Eftekhar., *et al*. evaluate the frequency, clinical presentation and cardiac involvement of children with RF in the North-East of Iran [8]. Derakhshan., *et al*. reported five-year experience with APSGN (Acute Post Streptococcal Glomerulonephritis) in south of Iran. APSGN was the most common type of glomerulonephritis in Shiraz, which usually has an uneventful course [9]. After 3 decades, GABHS pharyngitis diagnosed in 34.5% of cases with pharyngitis by rapid immunological GABHS antigen test in compare with 17.2% in conventional throat cultures. In some studies antibiotic susceptibility against GABHS were evaluated among Iranian population [10-12]. Complication of GABHS were investigated in previous studies [13-17]. PANDAS disorders (pediatric autoimmune psychiatric disorders) studied in 2 case control studies in Tehran [18,19].

In present study we tried to clarify the epidemiologic pattern of GABHS, prevalence of delayed immunologic post streptococcal disorders and antimicrobial susceptibility of GABHS among Iranian population.

Methods and Material

A retrospective /descriptive study had done by authors for determining the prevalence of GAS in Iran.

Inclusion criteria: We selected all Iranian studies which indexed between 2000 - 2015.

Target studies cases: All laboratory or medical reports about GAS in Iranian population in English or Persian (with English abstract).

Results

We reviewed 23 studies were performed in Iranian population. In nine studies prevalence of GABHS were assessed [3-5,20-25]. In seven investigations antibiotic susceptibility against GABHS were studied [10-12,25-27]. Role of GABHS in Torurette syndrome, psoriasis, PANDAS, ARF and PSGN were evaluated in other studies [6,8,9,18,19,28,29]. Comparing rapid test and conventional method for diagnosis of GABHS were considered in Noorbakhsh study in 2010 [29].

Group A beta-hemolytic streptococcus (GABHS) is an important etiologic agent of pharyngo-tonsillitis [30,31]. Post Streptococcal acute rheumatic fever is an important health problem among pediatric population.

In contrast to high income countries, serotypes of group A streptococci are still a major cause of pharyngitis and some post-infectious squeal such as rheumatic fever. Pediatric autoimmune neuropsychiatric disorders (PANDAS) associate with GABHS due to production of autoimmune antibodies. Recent evidence suggests that GABHS may increase the risk for obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), or tic disorder which has been termed PANDAS [16-18].

Acute post streptococcal glomerulonephritis (APSGN), one of the delayed side effect of streptococcal infection is the most common reason of inpatient pediatric glomerulonephritis.

Epidemics of food-borne pharyngitis due to group A Streptococcus are rarely reported [22]. Association between Psoriasis and GABHS infection is also described [29].

However, clinical diagnostic methods are not reliable [1,2]. Correct etiologic diagnosis and early treatment is very important for preventing the supportive and non-supportive complications of streptococcal pharyngo- tonsillitis [32,33]. Prevalence of streptococcal infection among children who presented with sore throat and prevalence of streptococcal carriage among asymptomatic persons is so important to inform physicians for making decisions despite of diagnostic laboratory tests in the presence of pharyngitis.

The most commonly used streptococcal antigens are anti streptolysin O (ASO) and antideoxyribonuclease [34]. These serologic tests are useful for diagnosing the streptococcal infections and also post streptococcal disease such as acute rheumatic fever and PSGN. Rapid test is other diagnostic method for detection of GABHS [35-39].

In a meta-analysis study the prevalence of streptococcal pharyngitis was 37%; and GAS carriage in Children (< 18 years) was 12% (95% CI: 9% - 14%). It concluded that the prevalence rates of GAS disease and carriage varied by age; children who were younger than 5 years had lower rates of GABHS induced pharyngitis [23].

As part of the worldwide effort to clarify the epidemiological pattern of group A streptococci in different countries, many different studies had done in Iran. GABHS and *S. pneumonia* had been searched as causative of pharyngitis of children in several studies [34-37,41-43]. Gharagozloo., *et al*. (1974) isolated beta-hemolytic streptococci in 26% of 578 patients with URTI; 74% were considered as viral [4], Fazeli., *et al*. (1999) assessed the prevalence of *Streptococcus pyogenes* serotypes in north of Iran (Gorgan province). In their study 65 isolate were positive for GABHS and 21 (32%) were M-type. Their profiles fell into four types with M1 predominating, which could reflect the presence of higher rate of rheumatic fever among school children in urban area and results showed a higher rate of colonization compared to those in rural areas [20].

Ghassemian., *et al.* reported all 85 isolates of *Streptococcus pyogenes* isolated from pharyngitis cases were sensitive to penicillin, amoxicillin, cephalexin and clindamycin, however 3 cases were resistant to penicillin. The resistance rate to erythromycin, tetracycline and ceftriaxone were 28, 46 and 3.5%, respectively. Erythromycin reported as drug of choice in Iranian patients who are allergic to lactams [27].

Discussion

The carriage rate of GABHS is varied in different part of Iran. First Gharagozloo., et al. (1974) isolated GABHS from 26% of 578 patients with URTI; 74% were considered as viral [4]; The most susceptible ages for streptococcal and viral pharyngitis were 5 - 8 and 2 - 6 years respectively. The streptococcal pharyngitis was common from late autumn to early spring. There was a positive correlation between the incidence of URTI and streptococcal isolation. In this study 86, 4, 2, 8 cases of isolates had group A, C, G and non typable streptococci respectively.

71 (82%) of group A strains were typable by agglutination ("T"-typing), but only 49 (57%) by precipitation ("M"-typing). Type one and twelve of "M" types were the most common type. 95% correlation was found between bacitracin disk and serologic method of hemolytic groups. All strains isolated were sensitive to penicillin, erythromycin and chloramphenicol, but 11 strains were resistant to tetracycline [4].

In 1970 Gharagozloo., *et al.* evaluated the bacitracin disk for identification of GABHS in throat cultures of 711 patients with positive beta-hemolytic streptococci [28]. These strains were grouped in parallel by the precipitin and bacitracin paper disk method. The former method was established as the standard by which the bacitracin technique was compared. The difference in results was about 5.67%. The greatest error (5.4%) was seen with non-group A strains being sensitive to bacitracin. In spite of this, it was shown to be advantageous to use the bacitracin disk for primary isolation from throat cultures rather than to consider all beta-hemolytic streptococci isolated as group A, which would give a magnitude of error around 16%.

The carriage rate in Zahedan (south east of Iran was 76/1092 [2]; in Urumia (North West of Iran) was 4.3, one of the lowest rates that have been reported in the region [24]. Ghaemi., *et al.* [21] reported 11% (175 strains) colonization rate in1588 healthy children between 6 - 12 years children lived in Gorgan (Eastern north of Iran); the carrier of GABHS in school aged children were more than the earlier age.

According to Fazeli., *et al.* study was done in 1999 between healthy school aged children in Gorgan province of 1588 taken throat swabs, 175 cases were positive for GABHS. Colonization of group A streptococci in urban children was higher than rural children. Of 65 positive isolates using standard techniques, 21 (32%) were M-type with M1 predominance reflecting existence of ARF in this area. 94% of isolates were positive for T-antigen with diverse pattern and T1 (26%) predominance and thenTB3264 (15%), TB\1-19 and B\25\1-19 (9.2%) and T2 and 2\28 (7.7%). The opacity factor was positive in 23(35%) of isolates. Results of serotyping studies in Iran could useful for developing a streptococcal vaccine [20].

Ghasemian., *et al*. reported 85 isolates of GABHS obtained from pharyngitis in Mazandaran (north of Iran) were sensitive to penicillin, amoxicillin, cephalexin and clindamycin except three cases with resistance to penicillin. 28, 46 and 3.5% of isolates were resistant to erythromycin, tetracycline and ceftriaxone respectively. Erythromycin reported as drug of choice in Iranian patients who are allergic to beta-lactams [27].

Jasir., *et al.* (2000) assessed carriage rate of GABHS between three groups of populations from the Tehran region and the North part of Iran (Gilan), among more than 5000 individuals with acute pharyngitis and healthy school children. Of 421 randomly selected isolates a predominance of M-types M4, M5, M11, M12, as well as the provisional type 4245; however, many of the isolates were T and M non- typable. 43% of isolates were negative for opacity factor. The distribution was different in comparison to previous report (1973-4), with M1and M12 predominance [5].

The carriage rate of group A beta-hemolytic streptococcus (GABHS) in Urumia (north west Iran) by Khashabi., *et al.* was 4.3%. There were no differences in the carriage rate between both sexes and two parts of the city. The results of this study show that the carriage rate of beta-hemolytic streptococcus is one of the lowest rates that have been reported in the area [24].

In Nourouzi., *et al*. study was done in Zahedan (south east of Iran) of 1092 specimens, 76 isolates were positive for GABHS, 98.68% were susceptible to cephalexin and cefazolin, 97.37% for erythromycin and 92.11% for penicillin with no statistically significant difference. 80.26% of isolates were susceptible to amoxicillin with significant difference ($p < 0.001$), erythromycin ($p = 0.001$) and penicillin ($p = 0.034$). They concluded that in spite of widespread resistance to antibiotics, penicillin still is the first drug of choice for treatment of GABHS pharyngitis and erythromycin is the best alternative drug for patients with allergy to penicillin [40].

In a recent study in Mashhad (Eastern of Iran), Sassan., *et al*. observed an extremely high prevalence of erythromycin resistance of GABHS [26]. The highest rate of erythromycin resistance for GABHS (98.8%) has been reported from China [25]. According to the report of CDC, the rate of erythromycin resistance of GABHS is not high in United States (8% - 9%) but 40%resistance rate were reported in Kerman (east of Iran) [8].

Sayyahfar., *et al*. found all strains were sensitive to penicillin G. The resistance rate against Erythromycin, Azithromycin and Clarythromycin, clindamycin and ofloxacin was 33.9%, 57.6% and 33.9%, 13.5% and 32.2% respectively [12].

Ardalan., *et al*. studied macrolide resistance in the base of molecular study among children. Fifty percent of isolates showed macrolide resistant, and 50% of them were M type (erythromycin resistant and clindamycin susceptible) [11].

Eftekhar., *et al.* evaluate the frequency, clinical presentation and cardiac involvement of children with RF in the North-East of Iran [8]. They reported a decreased frequency of RF in North-East Iran over the past few years. They concluded that carditis is endemic in this region. Considering the risk of morbidity after heart involvement, using the preventive program and suitable treatment is important [8].

Sarvghad., *et al*. reported an outbreak of food-borne tonsillopharyngitis in female dormitories in Iran. In a case-control assessment, throat swabs and hand specimens were obtained of food processing involved staff. 11 out of 17 throat swabs of students were positive for Streptococcus group A and also 2 specimens were positive in asymptomatic cooks. They found similar pattern in T agglutination and M protein factor (M3/T13) in strains of 11 students and 1 cook using DNA fingerprinting study. The result of this study showed epidemic food-borne

pharyngitis can occurs due to GABHS as well as group C and G. Therefore regular supervision on food processing is necessary for preventing food born outbreaks [22].

The results of recent study in Tehran (2009-10) diagnosed GABHS pharyngitis in 34.5% of cases by rapid strip test; 17.2% by pharyngeal culture. Inclusion criteria was acute onset of fever and pharyngitis .They excluded all diagnosed cases with acute pharyngitis except GABHS included viral pharyngitis (influenza, adenovirus, RSV; confirmed with rapid tests), allergic pharyngitis, referral pain (otitis media, teeth infection), 87 cases which had full inclusion criteria were studied. Throat swabs obtained from 87 remaining cases. Immuno chromatograhic Rapid Test Strip (ACON; Germany) and pharyngeal culture on conventional blood agar were used simultaneously to detect the GABHS from 87 cases. Culture plates incubated in CO2 incubator for 18 - 24 hours. GABHS was identified as gram-positive cocci isolated from beta hemolytic colonies. Bacitracin, SXT, Optochin, Biliary solubility; NACL 6.5% tests were used for differentiation of GABHS. Further complementary standard tests had done for diagnosis of other organisms (*S. pneumonia, N. meningitis, H. influenza*). There was no agreement between two methods ($P < 0.1$). The negative pharyngeal culture results are probably due to antibiotic usage in 43.2 % of patients. Positive rapid test results in pharyngeal swab was age dependent ($P < 0.05$). There was good correlation between observing the "petechia in pharynx of patients" and positive rapid test in pharyngeal swab ($P < 0.004$). Throat culture results were related to previous antibiotic usage in cases ($P < 0.03$). It concluded that rapid test in pharyngeal swab is helpful for rapid diagnosis and treatment of GABHS pharyngitis. Diagnosis of GABHS pharyngitis based on solely clinical findings is misleading in the majority of cases. Petechia observed in pharynx of the cases was highly predictive of streptococcal pharyngitis. Negative results in both methods are higher than expected in compare with other international references [36,38,39] but was very close to the previous studies in Iran. The carrier state for GABHS [30] in Iranian children were much lower than its rate in children living in developed countries (*S. pneumonia*: 21 - 59%) [30,36]. The high rate of Group G streptococci were reported in the recent Iranian studies [34,42,43]. Frequent antibiotic usage in Iran; exposure at different ages; different seasonality could be the reasons of this wide difference.

Sheikh., *et al*. (2010) in a Meta-analysis reported the prevalence of streptococcal pharyngitis and streptococcal carriage in Children in children who were younger than 18 years. The pooled prevalence of GABHS was 37% (95% confidence interval [CI]: 32% - 43%). Children who were younger than 5 years had a lower prevalence of GAS (24% [95% CI: 21% - 26%]). The prevalence of GAS carriage among well children with no signs or symptoms of pharyngitis was 12% (95% CI: 9% - 14%). It concluded that the prevalence rates of GAS disease and carriage varied by age; children who were younger than 5 years had lower rates of positive GABHS throat culture [23].

Association between Plaque-Type Psoriasis and perianal streptococcal cellulitis described by Rasi., *et al* [29].

Derakhshan., *et al*. reported 89% incidence rate for APSGN among 137 children diagnosed as AGN during 5 years in Southern Iran (Shiraz) Mean (SD) age in children with APSGN was 8.5 (range, 3.5-13) years, 117 (96%) children developed APSGN following a sore throat and 5 (4%) following an impetigo, with 95 (78%) during the cold seasons of the year. Anti streptolysin -O (ASO) titer was high in 84% of cases and C3 level was low in 86% of patients. There was no reported mortality but three cases presented by hypertensive encephalopathy. APSGN was the most common type of glomerulonephritis in Shiraz. It usually has an uneventful course usually following pharyngitis [9].

For determination the role of GABHS in PANDAS disorders (pediatric autoimmune psychiatric disorders) 2 case control studies had done in Tehran; Iran. All cases selected in pediatric neuropsychology ward and clinics in two referral hospitals (Rasoul and Aliasghar) affiliated by TUMS; Tehran, Iran (2008-2010).PANDAS cases included: cases with movement disorders (tic and tourett's disorders); cases with psychiatric manifestations (OCD; ADHD). Titer of antibodies against GABHS (ASOT, Anti-DNase B, and Anti streptokinase) compared between normal children and PANDAS cases. The antibody titers (IU/ml) in their area were compared and analyzed statistically. The area under ROC, sensitivity, specificity and positive predictive value of tests calculated.

Movement disorders: 53 children with tic (between 4 - 16 years) and 76 healthy controls (mean age = 9years) selected. There was significant difference between ASOT, Anti- DNase and Anti hyaluronidase titers among two groups ($p < 0.0001$; $p = 0.05$; $p = 0.002$). ASOT

(cut off level > 200 IU/ml) had 75% sensitivity; 84% specificity and 80% PPV; Anti- streptokinase (cut off level > 332 IU/ml) had 34% sensitivity; 85% specificity, and 90% PPV; Anti-DNase (cut off level > 140IU/ml) had 70% sensitivity; 99% specificity and PPV 90% [28].

Psychiatric disorders: 79 cases with OCD/ADHD disorder (mean age = 8.9 years) and 39 healthy controls (mean age = 9 years) studied. Most of cases studied in summer (57%) and spring (23%). ASOT, Anti-DNase and Anti hyaluronidase titers was higher cases (p = 0.000). ASOT (cut off level 195) had 90% sensitivity; 82% specificity, 'PPV 92%; AUC: (CI = %95; 0.99 - 0.91). Anti streptokinase: cut off level = 223) had 82% sensitivity; 82% specificity, PPV 95%; AUC: (CI = %95; 0.934 - 0.735).

AntiDNase (cut off level= 140) had 82% sensitivity; 82% specificity 'PPV 95%; AUC: (CI = %95; 0.99 - 0.91).

There are several studies in the literature about sensitivity and spasticity of GABHS diagnostic tests.

Leung., *et al*. showed most rapid tests have more than 95% and 90% sensitivity for antigen detection respectively, therefore positive rapid test is highly suggestive for GABHS pharyngitis, but negative test can't rule out the pharyngitis and needs confirmation by culture result [31].

Previously, latex agglutination test which was used as RADTs had low sensitivity but current tests based on enzyme immunoassay (EIA) techniques have higher sensitivity [3].

Tanz., *et al.* showed in their study, 70% sensitivity for RADT and as well as 30% positive cultures. Office culture sensitivity was significantly greater, 81% (range: 71% - 91%). Specificity of RADT was 98%, in compare to 97% specificity for office culture without any statistically significant difference. According to their results, sensitivity of RADT is lower than office culture significantly, but both tests isn't highly sensitive [44].

Gerber., *et al*. assessed the accuracy of various RADTs in the office setting [Gerber., *et al*. 2004]. Currently two RADTs are used for identifying streptococcal pharyngitis based on molecular biology methods with 86 - 94.8% sensitivity and 95 - 100% specificity but they are expensive. Recently different variant easy-to-perform RADTs are available for diagnosing GABHS pharyngitis [33].

In an Australian study for determine age-specific upper limit of normal (ULN) values of the ASO and ADB titres in children aged 4 - 14 years in urban Melbourne, the ULN for ASO titres in each age group was 120 (2.08 log units), 480 (2.68) and 320 (2.51). The ULN for ADB titres in each age group was 100 (2.00 log units), 400 (2.60) and 380 (2.58). The ASO and ADB ULN values in school-aged children are higher than the current reference ranges [34].

Conclusion

The carrier state for GABHS [34-37,40-42]; and *S. pneumonia* in Iranian children are much lower (3 - 6%) than its rate in children living in developed countries (*S. pneumonia* : 21 - 59%) [30-32]. The high rate of Group G streptococci were reported in the recent Iranian studies [9-12]. Frequent antibiotic treatment in Iran; exposure at different ages; different seasonality could be the reasons for this wide differences. Diagnosis of streptocoocal pharyngitis only based on clinical findings are misleading in most times. Presence of "petechia in pharynx" was highly suspecious for streptococcal pharyngitis in cases. Adding the rapid stript test in pharyngeal swab are helpful for rapid diagnosis and treatment of streptococcal pharyngitis. Rapid immunological GABHS antigen test in compare with conventional throat cultures, showed higher advantage for diagnosis especially in the cases with previous antibiotic usage. Patients with PANDAS (OCD and ADHD disorder; tic disorder) had a significant high antibody titer against GAS in compare to healthy children. It presents possible role for streptococcal infection in tic disorders. Treatment of streptococcal infection is available by using of long acting Penicillin in our country. Use of aggressive treatment like plasmapheresis etc needs future RCT studies.

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