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소아에서 분리된 A군 연쇄구균의 *emm*형 분포 연구

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이 논문을 의학석사학위논문으로 제출함

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최재홍의 석사학위 논문을 인준함

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Abstract

Distribution of *emm* types among Group A Streptococcus isolates from children

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Background: Group A streptococcus (GAS) is a common human pathogen responsible for a wide spectrum of diseases. The variation in the predominant *emm* type is known to able to affect the incidence and clinical manifestations of GAS infections. Recently, increase of invasive GAS infections and several outbreaks of scarlet fever have been reported in several countries. We investigated the clinical characteristics and molecular epidemiology of GAS infection in Korea.

Method: GAS strains previously obtained from clinical isolates at the Seoul National University Children's Hospital between 1991 and 2012 and the Seoul National University Bundang Hospital between 2006 and 2012 were analyzed. The clinical characteristics were reviewed by medical records and antimicrobial resistance was investigated by disk diffusion test and E-test. The *emm* genotypes and pyrogenic exotoxin genes (*spe*A, *spe*B, *spe*C) were identified using polymerase chain reaction (PCR) and sequencing.

Results: A total of 155 GAS cases were investigated. Among these cases, the clinical diagnosis was as followed: pharyngitis 44 (28.4%), scarlet fever 41 (26.5%), noninvasive skin and soft tissue infection (SSTI) 37 (23.9%), invasive disease 19 (12.3%), poststreptococcal glomerulonephritis (PSGN) 4 (2.6%), rheumatic fever 2 (1.3%), and others 8 (5.2%). All GAS isolates were sensitive to penicillin. The erythromycin resistance rate was 10.3% (16/155), and all isolates during the recent 3 years were susceptible to erythromycin. The most prevalent *emm* types were *emm*1 (19.4%), *emm*12 (18.7%) and *emm*4 (18.1%). Distribution of *emm* genotype differed according to clinical disease. The *emm*1 was most common (47.4%) in invasive GAS infections and *emm*4 was most common (48.8%) in scarlet fever. The *emm*12 was the most common type in pharyngitis (25.0%) and SSTI (29.7%). During the recent 3 years, there was an increase in invasive GAS infections and scarlet fever which was correlated with an increase in specific *emm* types, *emm*1 and *emm*4, respectively. According to the analysis of exotoxin genes, *speB* was found in all isolates and *spe*A and *spe*C genes were detected in 36.8% and 49.0% of the isolates, respectively. The *spe*C detection rate was high (65.9%) in scarlet fever compared to other GAS infections (P=0.017).

Conclusion: There has been a recent increase in invasive GAS infections and scarlet fever associated with an increase of *emm*1 and *emm*4, respectively. Changes in prevalent GAS genotypes and diversity in disease emphasizes the importance of continuous surveillance on clinical and molecular characteristics of GAS.

Keywords: *Streptococcus pyogenes*, Group A Streptococcus, streptococcal M protein, exotoxin

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List of Abbreviations

CDC, Centers for Disease Control and Prevention

CLSI, Clinical and Laboratory Standards Institute

emm, M protein gene

GAS, Group A Streptococcus

PSGN, poststreptococcal glomerulonephritis

SNUBH, Seoul National University Bundang Hospital

SNUCH, Seoul National University Children's Hospital

spe, streptococcal pyrogenic exotoxin

SSTI, skin ans soft tissue infection

STSS, streptococcal toxic shock syndrome

1. Introduction

Group A streptococcus (GAS) is a gram-positive pathogen in humans. GAS infections are a worldwide problem and have been estimated to be responsible for approximately 600 million cases of pharyngitis each year (1). Besides pharyngitis, GAS causes a broad spectrum of diseases, including impetigo, scarlet fever, toxic shock syndrome, and invasive diseases such as septicemia, necrotizing fasciitis, osteoarticular infection, and meningitis.

Several virulence factors of GAS have been identified and include the M protein, lipoteichoic acid, streptolysin, and pyrogenic exotoxins (2). Among these factors, the M protein, which is located on the bacterial surface, plays an important role in the pathogenesis of this microorganism. It is encoded by the *emm* gene and serves as an important epidemiological marker in GAS infections. GAS strains are typed by sequencing the 5′ hypervariable region of the *emm* gene. More than 120 distinct *emm* types have been identified (3). The *emm* type distributions of GAS differ across geographical regions, and the incidence and clinical manifestations of GAS infections are associated with variations in the predominant *emm* types (4). Recently, an increase in invasive GAS infections and outbreaks of scarlet fever has been reported in several countries (5-8).

This study analyzed the clinical and molecular characteristics of GAS infections diagnosed in children during the past 22 years in Korea. We focused our analysis on the distribution of *emm* types, changes in the

antimicrobial resistance rate, and the presence of specific pyrogenic exotoxin genes.

2. Materials and Methods

2.1 Study Design

GAS isolates that were obtained from children under the age of 18 years were included in the microbiology lab databases of the Seoul National University Children's Hospital (SNUCH) from 1991 to 2012 and the Seoul National University Bundang Hospital (SNUBH) from 2006 to 2012. These isolates were prospectively collected through a hospital-wide surveillance system and were stored at -70°C. GAS isolate collection periods differed for different diseases. For example, isolates of invasive infections and non-invasive skin and soft tissue infections (SSTI) were collected from 1991 onwards, whereas isolates from scarlet fever and pharyngitis were collected from 2002 onwards. The number of GAS isolates also varied by year. Before 2002, only 21 isolates (13.5% of the total) were collected; and so, several analyses included GAS isolates from after 2002. Demographic information of the patients and details of their underlying diseases, clinical diagnoses, and outcomes were collected from medical records. The clinical diagnoses included pharyngitis, non-invasive SSTIs, scarlet fever, poststreptococcal glomerulonephritis (PSGN), rheumatic fever, and invasive diseases. Non-invasive SSTIs included cellulitis, impetigo, lymphadenitis, and peritonsillar abscesses. Invasive disease was defined as the isolation of GAS from a normally sterile body fluid such as blood, cerebrospinal fluid, pleural fluid, pericardial fluid, joint fluid, bone aspirate, or a deep tissue abscess (9).

2.2 Bacterial Isolates and Antibiotic Resistance

Identification of GAS isolates and antimicrobial susceptibility tests were performed using automated microbiology systems, including Vitek-1 (BIOMÉRIEUX; Marcy l'Etoile, France) and MicroScan Walk-Away (Siemens Healthcare Diagnostics; Deerfield, IL, USA). GAS isolates were confirmed by β-hemolysis on sheep blood agar, colony size, and the bacitracin susceptibility test. Antimicrobial susceptibility tests were performed for penicillin, vancomycin, erythromycin, and clindamycin by the disc diffusion test and the E-test. The breakpoints used to determine the susceptibility of GAS strains to antibiotics were those recommended by the Clinical and Laboratory Standards Institute (10): susceptible, intermediate, or resistant. Macrolide resistance phenotypes were classified as $cMLS_B$ (constitutive macrolide, lincosamide, and streptogramin B), $iMLS_B$ (inducible) and M phenotype (resistant to erythromycin, sensitive to clindamycin). The double disk synergy test for erythromycin and clindamycin was performed to determine the inducible resistance.

2.3 *emm* Typing

GAS *emm* typing was performed according to the protocol of the Centers for Disease Control and Prevention (CDC) (11). DNA from GAS isolates was purified using the AccuPrep Genomic DNA Extraction kit (Bioneer; Cheongwon, Korea). Sequencing reactions were performed in the DNA Engine Tetrad 2 Peltier Thermal Cycler (BIO-RAD) using the ABI BigDye(R) Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) in Macrogen Co. (Seoul, Korea). The hypervariable region of the *emm* gene encoding the

amino-terminal terminus of the M protein was amplified by PCR by using the primers 1 (5′-TATT(C/G)GCTTAGAAAAATTAA) and 2 (5′-GCAAGTTCTTCAGCTTGTTT). Single pass sequencing was performed on each template using these primers. Sequencing reactions were analyzed with the sequencherTM 5.1 (Gene Codes Co; Ann Arbor, MI, USA). The analyzed sequences were compared with the *emm* database at the CDC website to determine the *emm* type (12).

2.4 Exotoxin Genes

GAS isolates were tested for the presence of streptococcal pyrogenic exotoxin (*spe*) A, *spe*B and *spe*C by PCR with primer pairs specific to each gene (13). The primers used for *spe* genotyping were: *spe*A (5′-ACTTAAGAACCAAGAGATGG, 5′-CCTTATTCTTAGGTATGAAC), *spe*B (5′-GGATCCCAACCAGTTGTTAAATCTCT, 5′-AACGTTCTAAGGTTTGATGCCTACAA), and *spe*C (5′-AAGTGACTCTAAGAAAGACA, 5′-TTGAGTATCAATGTTTAATG).

2.5 Statistical Analysis

Differences between categorical variables were tested using the chi-square or Fisher's exact test. All data were analyzed using SPSS version 20.0, and the results were considered statistically significant when the *P* value was less than 0.05.

2.6 Ethics Statement

This study was approved by the institutional review board of the Seoul National University Hospital (No.H-1302-059-464) and the Seoul National University Bundang Hospital (No.B-1303-194-301). The need for informed consent was waived.

3. Results

3.1 Demographic and Clinical Characteristics

A total of 155 isolates from children with proven GAS infection were included in this study. The median age of the children was 5.5 years (range 0—18 years), and 91 (58.0%) were boys. Of the patients, 9 (5.7%) were immunosuppressed. These included transplant recipients (n = 4), children being treated with chemotherapy for malignancy (n = 3), and those diagnosed with juvenile rheumatic arthritis (n = 1) and nephrotic syndrome (n = 1). The clinical diagnoses included pharyngitis in 44 cases (28.4%), scarlet fever in 41 cases (26.5%), non-invasive SSTIs in 37 cases (23.9%), invasive diseases in 19 cases (12.3%), PSGN in 4 cases (2.6%), rheumatic fever in 2 cases (1.3%), and others such as otitis media or wound infection after operation in 8 cases (5.2%).

The median ages of patients with pharyngitis, scarlet fever, and non-invasive SSTI were 7.8 years, 5.2 years, and 4.9 years, respectively. All isolates from pharyngitis and scarlet fever patients were obtained from throat cultures, and isolates from non-invasive SSTI patients from wound cultures or pus aspirations. In all cases of PSGN and rheumatic fever, GAS was isolated from throat cultures.

A total of 19 children (14 boys [73.7%] and 5 girls [26.3%]) were diagnosed with invasive GAS infections. Four patients had underlying diseases, including congenital hepatic fibrosis, Pierre-Robin syndrome, chylothorax, and Sturge-Weber syndrome. However, all 19 patients were immunocompetent. Their median age was 3.9 years (0—14.9 years).

Among all patients, 63.2% were under 5 years of age and 31.6% were under 1 year of age. The portion of cases under 1 year of age was higher among patients with invasive GAS infections than among those with non-invasive infections (6/19 vs. 3/136, P <0.001). Osteoarticular infection and invasive SSTI were the most common diagnoses (5 patients, 26.3%), followed by bacteremia without focus in 3 patients (15.8%) and streptococcal toxic shock syndrome (STSS) in 2 patients (10.5%). The remaining 4 patients were diagnosed with pneumonia, central nervous system infection, pericarditis, and peritonitis respectively. Among all invasive infections, 9 patients underwent surgeries, and none of the patients died of invasive GAS infections.

3.2 Antimicrobial Resistance

All GAS isolates were susceptible to penicillin. Erythromycin resistance was found in 16 (10.3%) and clindamycin resistance in 10 (6.5%) of the isolates. Among erythromycin-resistant isolates, 10 (62.5%) were classified as the $cMLS_B$ phenotype, 4 (25.0%) as $iMLS_B$, and 2 (12.5%) as the M phenotype. Regarding the *emm* type, 37.5% of the isolates with erythromycin resistance were *emm*28 and 31.3% were *emm*12. In respect to the clinical diagnoses, 18.2% (8/44) of isolates derived from patients with pharyngitis and 16.2% (6/37) of those derived from patients with non-invasive SSTI were resistant to erythromycin. None of the invasive GAS isolates were resistant to erythromycin. In samples isolated before 2009, 14.2% (16/113) were resistant to erythromycin; however, from 2010 to 2012, all GAS isolates were susceptible to erythromycin (Fig 1).

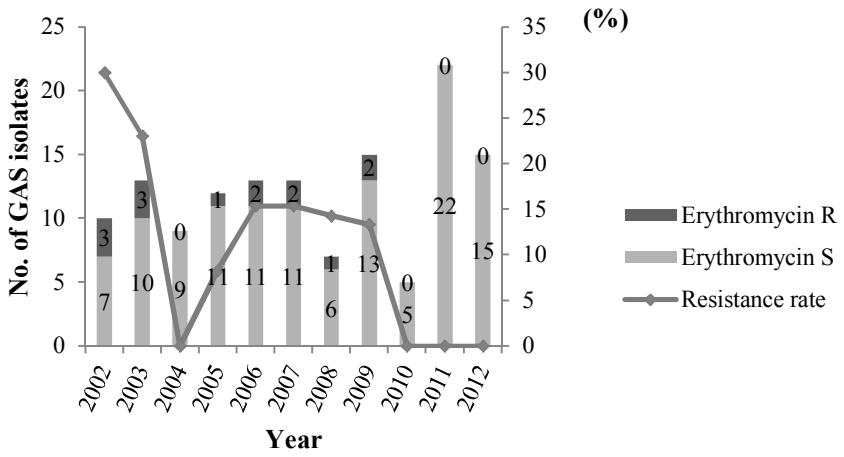

Figure 1. Yearly trend of erythromycin resistance among GAS isolates from 2002-2012

3.3 *emm* Sequence Typing

In our study, 21 different *emm* types were identified. The 6 most prevalent *emm* types were *emm*1 (19.4%), *emm*12 (18.7%), *emm*4 (18.1%), *emm*3 (9.7%), *emm*22 (7.1%), and *emm*89 (6.5%) (Table 1). Among these, *emm*1, *emm*12, and *emm*4 accounted for 56.1% of all isolates.

Among the 19 invasive GAS isolates in our study, *emm*1 was the most common (identified in 9 cases [47.4%]), followed by *emm*3 (identified in 5 cases [26.3%]) (Fig 2). The prevalence of *emm*1 in invasive GAS infections was higher than in non-invasive infections ($P = 0.003$). Moreover, 47.4% (9/19) of all invasive infections were reported in 2011 and 2012. During these 2 years, 8 cases (88.9%) were identified as the *emm*1 type and 1 case as the *emm*3 type (Fig 2). All 6 cases in 2012 were found in the Gyeonggi province.

Among 41 strains isolated from patients with scarlet fever, the *emm*4 type was the most common (identified in 20 cases [48.8%]), followed by the *emm*3 type (identified in 6 cases [14.6%]) (Fig 3). *emm*4 was the predominant *emm* type (100%) found in patients with scarlet fever from 2010-2012. Among 44 pharyngitis isolates, 13 different *emm* types were detected, and *emm*12 was the most common type (identified in 11 cases [25.0%]), followed by *emm*1 (identified in 6 cases [13.6%]) and *emm*3 (identified in 4 cases [9.1%]). Among 37 non-invasive SSTI cases, 9 different *emm* types were detected, with *emm*12 being the most common type (identified in 11 cases [29.7%]), followed by *emm*1 (identified in 9 cases [24.3%]), and *emm*4 (identified in 5 cases [13.5%]). In pharyngitis and non-invasive SSTI cases, the *emm*

distribution varied over the years and did not exhibit a significant yearly trend.

3.4 Exotoxin genes

The *spe*B gene was detected in all GAS isolates, whereas the *spe*A and *spe*C genes were detected in 36.8% (57/155) and 49.0% (76/155) of the isolates, respectively (Table 2). The *spe*C gene was identified in 27 isolates of 41 patients with scarlet fever (65.9%). The *spe*C gene detection rate was significantly higher for isolates from scarlet fever than that for other GAS infections (65.9% vs. 43.0%, respectively, $P = 0.017$). We observed differences in the exotoxin gene detection rate depending on specific *emm* types. *emm*4 (89.3%, 25/28), *emm*22 (100%, 11/11), and *emm*89 (88.9%, 8/9) had high detection rates for *spe*C, whereas *emm*1 (6.7%, 2/30), *emm*3 (6.7%, 1/15), and *emm*44 (0.0%, 0/6) had low detection rates (Table 2). The *spe*A gene did not show exhibit a predominance within a specific disease; however, 85.7% (6/7) of *emm*28 isolates were positive for *spe*A (Table 2).

Table 1. emm type distribution in children with GAS infections from 1991 to 2012

	Number (%)
emm 1	30 (19.4)
emm 12	29 (18.7)
emm 4	28 (18.1)
emm 3	15 (9.7)
emm 22	11 (7.1)
emm 89	10 (6.5)
emm 28	7 (4.5)
emm 44	6 (3.9)
emm 78	3 (1.9)
Others*	16 (10.3)
Total	155

Others*: *emm*6 (n = 2), *emm*18 (n = 2), *emm*75 (n = 2), *emm*87 (n = 2), *emm*23 (n = 1), *emm*29 (n = 1), *emm*49 (n = 1), *emm*50 (n = 1), *emm*80 (n = 1), *emm*81 (n = 1), *emm*94 (n = 1), *emm*102 (n = 1)

Figure 2. *emm* type distribution and yearly trend of invasive GAS infections

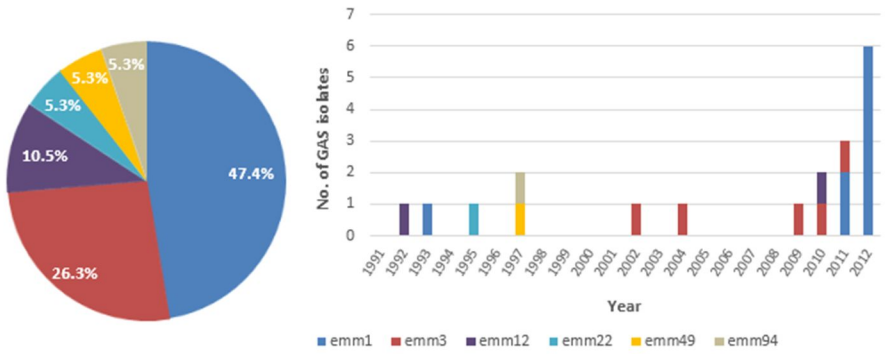

Figure 3. *emm* type distribution and yearly trend of scarlet fever from 2002 to 2012

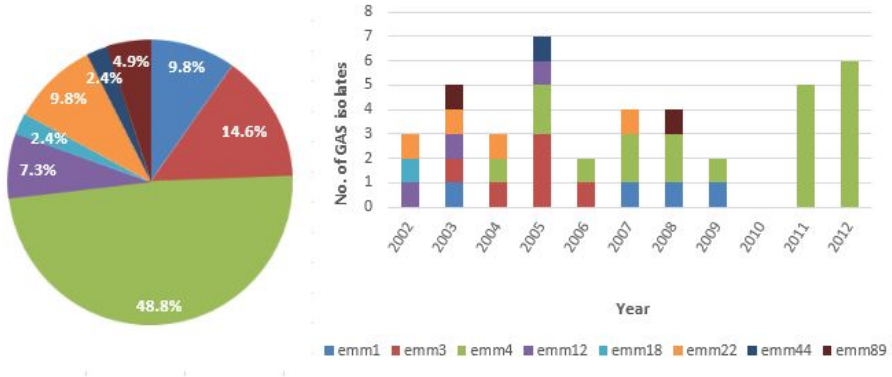

Table 2. Pyrogenic exotoxin and *emm* type

emm type	*spe*A		*spe*B		*spe*C		Total
	Positive (%)	*P*	Positive (%)	*P* value	Positive (%)	*P* value	
emm 1	12 (40.0%)	-	30 (100%)	-	2 (6.7%)	<0.001	30
emm 12	9 (31.0%)	-	29 (100%)	-	11 (37.9%)	-	29
emm 4	6 (21.4%)	-	28 (100%)	-	25 (89.3%)	<0.001	28
emm 3	7 (46.7%)	-	15 (100%)	-	1 (6.7%)	0.001	15
emm 22	5 (45.5%)	-	11 (100%)	-	11 (100%)	<0.001	11
emm 89	3 (30.0%)	-	10 (100%)	-	9 (90.0%)	<0.001	10
emm 28	6 (85.7%)	0.010	7 (100%)	-	6 (85.7%)	-	7
emm 44	3 (50.0%)	-	6 (100%)	-	0 (0.0%)	0.028	6
Others*	6 (31.6%)		19 (100%)	-	11 (57.9%)	-	19
Total	57 (36.8%)		155 (100.0%)		76 (49.0%)		155

Others*: *emm*78, *emm*6, *emm*18, *emm*75, *emm*87, *emm*23, *emm*29, *emm*49, *emm*50, *emm*80, *emm*81, *emm*94, *emm*102

4. Discussion

In this study, we analyzed *emm* types among GAS strains isolated from children diagnosed with various diseases during the past 22 years. We found a predominance of *emm*1 for invasive GAS infections and of *emm*4 for scarlet fever. The resistance rate for erythromycin was low (10.3%), and from 2010 to 2012, none of the isolates was resistant to erythromycin.

The distribution of *emm* types is known to differ between countries. A possible explanation for this might be differences in economic status or climates, as both are associated with differences in the prevalence of clinical diseases (4). In our study, the total distribution of *emm* types was similar to that of high-income countries (4), and the distributions of the 3 most common *emm* types (*emm*1, *emm*12, and *emm*4) were similar to the distributions that have been reported in Asian countries (14). However our results are different from the distribution rates reported in Africa and the Pacific area.

Since the 1980s, an increase in invasive GAS infections has been reported worldwide (15, 16). Many studies have shown that *emm*1 and *emm*3 are associated with invasive diseases and with high mortality rates. A predominance of the *emm*1 type in invasive infections was noted in European countries and the United States, and the *emm*3 type was ranked second among invasive GAS isolates in many countries (17-19). The *emm* type distribution in this study was similar to that reported in other countries. In this study, *emm*1 was the most common type in 47.4%, followed by *emm*3 in 26.3% of invasive isolates. Interestingly, 47.4% (9/19) of invasive infections were

identified in isolates collected in 2011 and 2012, and 88.9% (8/9) of these isolates during this period were identified as the *emm*1 type.

There are several risk factors known to be associated with invasive GAS infections. These include a preceding varicella zoster or influenza infection, age, and the use of non-steroidal anti-inflammatory drugs (20-24). In particular, a higher incidence of invasive GAS infections has been observed in children under the age of 1 year (23, 24). In this study, 31.6% of children (6/19) were under the age of 1 year, and the high incidence of invasive GAS infections was associated with an age of below 1 year (P <0.001). As this was a retrospective review, we could not obtain any information about other risk factors.

Outbreaks of scarlet fever have been reported worldwide. In Mexico, an outbreak of scarlet fever occurred in 1999, and *emm*2 was the most common identified GAS type (25). In 2011, scarlet fever outbreaks occurred in Hong Kong and Shanghai, China, and molecular studies showed a predominance of the *emm*12 type (26, 27). In our study, we found a predominance of the *emm*4 type for scarlet fever, and interestingly, all 11 strains isolated in 2011 and 2012 were identified as the *emm*4 type. According to the Korean Disease Web Statistics System (28), case reports of scarlet fever have dramatically increased since 2011. Although the case definition for reporting the disease changed from “confirmed” to “confirmed and suspected” since September 2012, the specific *emm* predominance among recent scarlet fever GAS isolates suggests the possibility of a scarlet fever outbreak associated with *emm*4.

Scarlet fever is well known as a toxin-mediated disease. The clinical manifestations of scarlet fever, including the strawberry tongue and scarlatiniform rash are known to be associated with the production of pyrogenic exotoxins, but a strict association between scarlet fever and exotoxins is not always found (29). Recently, a study in Portugal demonstrated that the exotoxins *spe*A and *spe*C were associated with scarlet fever cases. And *emm*87, *emm*4, and *emm*3 were overrepresented in scarlet fever GAS isolates in that study (29). Our results show that the exotoxin *spe*C was associated with scarlet fever isolates. Moreover, several *emm* types (such as *emm*4, *emm*22, and *emm*89) showed high positive rates for the *spe*C gene. The changes in *spe*C related *emm*-types could have an impact on scarlet fever epidemiology.

We found a considerable diversity regarding *emm* types for pharyngitis. *emm*12 and *emm*1 were the most common types and accounted for 38.6% of all isolates. This diversity and distribution of *emm* types is similar to those in most reports from United States and Asia, including those in previous reports on Korean children (30-32).

To date, all GAS isolates have been shown to be sensitive to penicillin. However, in patients with a penicillin allergy, macrolides could be the second treatment choice for GAS infections. Worldwide resistance rates of GAS to macrolides were reported to range from 2.6% to 97.6% (33-36). In Korea, erythromycin-resistant GAS isolates accounted for 28.5% to 51% of cases in the early-2000s (37-39). However, in the mid-2000s, erythromycin resistance rates of 4.9% to 9.8% were reported (40, 41). In our study, 10.3% of GAS

isolates showed resistance to erythromycin. Moreover, none of the GAS isolates collected from 2010-2012 were resistant to erythromycin. Up to the early 2000s, the increase in erythromycin resistance was reported to be associated with antibiotic pressure caused by the increase in macrolide consumption in many countries (42). However, there have been recent reports, including those in Korea, of decrease in erythromycin resistance rates despite an increase in consumption of macrolides (40). Several *emm* types have been reported to show a strong association with erythromycin resistance; however, there is a discrepancy between reports from different countries and at different periods (40). Erythromycin resistance rates were reported to be over 87.5% and 91.8% for *emm*12 in Korea and China, respectively (43, 44). However, the erythromycin resistance rate was variable for *emm*12 in Spain, and in our study, the rate was 16.7% of total *emm*12 (45). In Spain, *emm*4 showed a high erythromycin resistance rate; however, only 1 isolate of 28 *emm*4 strains (3.6%) in our study was erythromycin-resistant. Further studies on the determinants of erythromycin resistance for GAS are needed.

Our study has several limitations. It included 2 university hospitals located in 2 different cities, and the data of only 2 cities (Seoul and Seongnam) are not representative of the national GAS epidemiology. Moreover, both hospitals are tertiary referral centers. This might have affected the cases included in this study, and the number of non-invasive SSTIs, pharyngitis, and scarlet fever could have been underestimated. The usage of previously collected isolates could lead to an unequal annual distribution, especially in earlier years. For example, 86.5% of total GAS isolates were collected after

2002. In addition, clinical data such as comorbid status, history of recurrent pharyngitis, and other risk factors were not fully investigated.

4.1 Conclusions

To date, there have been relatively few reports of GAS infections, and the data on the *emm* distribution in Korean children are limited. In this study, we analyzed the *emm* types, pyrogenic exotoxins, and antimicrobial resistance of GAS isolates obtained during the past 22 years in children. We found a recent increase in invasive GAS infections during in 2011 and 2012 that was associated with an increase in the *emm*1 type. We also observed *emm*4 predominance in scarlet fever cases, and all isolates collected in 2011 and 2012 were *emm*4. Moreover, a recent decrease in erythromycin resistance was noted. In conclusion, changes in prevalent GAS genotypes and diversity in disease emphasize the importance of continuous surveillance of the clinical and molecular characteristics of GAS.

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국 문 초 록

A군 연쇄구균은 소아에서 흔한 감염균 중 하나이며, 최근 세계 각국에서 침습성 감염의 증가와 성홍열의 유행이 보고되어 관심이 높아지고 있다. A군 연쇄구균의 주요 병인자중 하나인 M 단백의 *emm* 유전형의 차이에 따라 A군 연쇄구균의 임상적 특징이 달라지는 것이 어느 정도 알려져 있어, 본 연구에서는 국내에서 *emm* 유전형에 따른 임상적 특징과 역학에 대해 알아보고자 하였다.

서울대학교 어린이병원 (1991~2012년)과 분당서울대학교 병원 (2006~2012년)에서 전향적으로 수집된 임상적인 의미가 있는 A군 연쇄구균을 이용하였다. 균주에 대해서는 PCR을 이용하여 *emm* 유전형과 외독소 (*spe*A, *spe*B, *spe*C)를 분석하였고, 원판 확산법과 E-test를 이용하여 항생제 감수성을 확인하였다. 의무기록 분석을 통해 각 균주가 일으킨 질환의 임상적 특징을 조사하여 종합 분석하였다.

총 155개의 A군 연쇄구균을 분석하였으며, 각각의 임상진단은 인후염 44건 (28.4%), 성홍열 41건 (26.5%), 피부 연조직 감염 37건 (23.9%), 침습성 감염 19건 (12.3%), 연쇄구균감염후 사구체신염 4건 (2.6%), 류마티스 열 2건 (1.3%), 기타 8건 (5.2%)이었

다. A군 연쇄구균은 모두 페니실린에 감수성을 보였으며, 에리스로마이신 내성률은 10.3% (16/155)이었다. 본 연구에서 총 21종류의 *emm*형이 확인되었으며, 흔한 *emm*형은 *emm*1 (19.4%), *emm*12 (18.7%), *emm*4 (18.1%) 순으로 나타났다. 침습성 감염에서는 *emm*1형이 가장 흔하였고 (47.4%), 성홍열을 일으킨 균주에서는 *emm*4 (48.8%)가 가장 흔하였다. 최근 3년 (2010~2012년) 동안 침습성 감염의 증가는 *emm*1의 증가와 연관되었다. 외독소 유전자는 *spe*A (36.8%), *spe*B (100.0%), *spe*C (49.0%)로 각각 검출되었으며, 그 중 *spe*C는 성홍열 균주와 연관되었다. (65.9%, P=0.017)

본 연구에서 약 20여년 동안 소아에서 분리된 A군 연쇄구균의 M 단백 *emm* 유전형을 통하여 시기별 분포와 항생제 감수성의 변화 추이를 분석하였으며, *emm* 유전형이 특정 임상 양상과 연관되어 있으며, 독소 유전자의 분포와도 연관성이 있음을 확인하였다.

주요어: A군 연쇄구균, *emm*형, 외독소

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