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CLINICO - MICROBIOLOGICAL STUDY OF INVASIVE GROUP A STREPTOCOCCAL (GAS) DISEASE IN SOUTHERN INDIA

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ABSTRACT Group A streptococcal (GAS) associated-disease and sequalae are a significant public health concern in India, contributing to high morbidity and mortality in children and young adults. Despite their widespread prevalence, comprehensive data on incidence and endemicity of infections of invasive GAS disease across the country is lacking. The need for extensive GAS epidemiological data is vital to the effective prevention and management of streptococcal disease in India. The following study conducted over a period of five years, at CMC Vellore, correlates the microbiological and clinical aspects of the disease as seen in this tertiary care center in southern India. This is intended to provide useful information to clinicians as well as microbiologists especially for those who are concerned with the management and control of GAS disease in India.

BACKGROUND: Invasive group A streptococcal disease has attracted much attention globally for several decades; however, despite the endemicity of streptococcal infections, its reported literature from India is scanty.

AIM: This study was undertaken to describe the clinical and microbiological aspects of streptococcal invasive disease among patients seen in a south Indian tertiary care center and identify measures to control them.

MATERIALS AND METHODS: Fifty seven group A streptococci recovered from an equal number of patients were selected for the study. Invasive streptococcal disease was defined by the isolation of group A streptococci from sterile body sites with diverse clinical signs and symptoms. Isolates were subjected to emm typing by an automated gene sequencing method and analyzed in relation to the demographic / clinical details of patients and outcome of their management.

RESULTS: Highest incidence was found among elderly patients (26.3%) followed by neonates (21%). Thirty four (59.6%) were blood isolates and 31 (54.3%) had underlying conditions such as diabetes mellitus and malignancy (12.3% each). Forty two emm types were identified among 57 isolates with types 63, 74, 85 and 110 accounting for 21.05 %; one type was a hitherto unrecognized. There was no association of any type with particular clinical condition. Thirteen of the 55 patients expired of whom nine had underlying conditions. Twelve different emm types were associated with them.

CONCLUSION: Close clinical and laboratory monitoring of patients especially neonates and elderly patients with underlying conditions is necessary to identify and control severe group A streptococcal invasive disease in regions endemic to group A streptococcal infection.

KEYWORDS : GAS; iGAS;*emm* types

INTRODUCTION

Emergence of severe group A streptococcal invasive disease (iGAS) has attracted a lot of attention in western countries for the past several years [1-4]. Despite aggressive antibiotic treatment, rapidly progressing conditions such as bacteremia, necrotizing fasciitis (NF), meningitis and streptococcal toxic shock syndrome (STSS) often lead to high mortality. Several extracellular products including streptococcal pyrogenic exotoxins and super antigens are believed to play an important role in their pathogenesis [5]. Characterization of GAS by *emm* typing has shown that types 1, 3, 12, and 28 are the most predominant types associated with iGAS [6, 7]. However recent studies from Europe and developing countries have confirmed high heterogeneity among *emm* types associated with iGAS [8, 9]. Interestingly, the *emm* type profile in endemic regions is different from those reported from developed countries [10-12]. These differing epidemiological features of iGAS will have significant implications in their prevention and should be taken into consideration while finalizing vaccine strategies.

For decades, researchers in India focused their attention on sequelae such as acute rheumatic fever / rheumatic heart disease (RF/RHD) and thus very little information is available on the prevalence of iGAS. To the best of our knowledge there are only two reports on invasive disease from India, besides two case reports on septic arthritis and toxic shock syndrome [12-15]. The objective of this study is to describe the clinical profile of iGAS and the distribution of *emm* types causing them among south Indian patients so as to identify appropriate methods to manage and control these conditions.

MATERIALS AND METHODS

Fifty seven non-repetitive Group A Streptococci (GAS) recovered from various sterile sites of patients seen at a tertiary care center in southern India during January 2000 and July 2007 were subjected to further characterization by *emm* typing. All GAS recovered from sterile body sites were classified as invasive isolates. The patients were classified into various clinical syndromes by their clinical details, underlying conditions and other epidemiological data obtained from their medical charts after obtaining necessary administrative approval. All isolates preserved by lyophilization was confirmed as GAS by micro-nitrous acid extraction co-agglutination method and were subjected to further characterization by *emm* typing [16- 18]. Genotypes were analyzed in relation to the clinical details of patients. Institutional Ethics Committee approval was obtained for conducting this study.

RESULTS

Age and sex-wise analysis of 57 patients with iGAS showed that the highest incidence was seen among the age group of 51 to 65 years (n = 15) followed by neonates (n = 12) **(Table 1)**. In general there was predominance among males (68.4%). Thus 19 (33.3%) of 57 cases were seen among males aged >50 years of age, followed by neonates (14%).

Blood isolates accounted for 34 (59.6%) of the 57 GAS isolates followed by peritoneal fluid (n=7), CSF and pleural fluid (5 each), bleb (3) and synovial fluid/bile (1 each) (Data not shown).

Table 2 shows the clinical syndromes seen among patients with invasive disease. Cases of sepsis (n = 13), meningitis (n = 9) and peritonitis (n = 8) accounted for 30 (52.6%) of the 57 cases. There were two cases from whom a final clinical diagnosis could not be obtained.

Underlying conditions were identified in 31(54.4%) of the 55 cases. In two cases, the presence or absence of such conditions was not available **(Table 3)**. Malignancy and diabetes mellitus were the most predominant (12.3% each).

Thirty one (96.8%) of the 32 cases with underlying clinical conditions were seen among patients >21 years of age; 21 (65.6%) of these were seen among those above 51 years of age **(Table 4)**.

A total of 42 *emm* types were identified among 57 GAS isolated from invasive diseases **(Fig 1).** Four types namely, 63, 74, 85 and 110 (3 each) accounted for 12 (21.05 %) of the 57 GAS isolates. Five (0.12 %) of the 42 types identified belonged to sequence types (st); one type (stKNB6) was a hitherto unrecognized new type at the time of the study. Multiple types were isolated from different specimens and there was no definite association of any type with any particular clinical specimen **(Table 5)**.

Thirteen (23.6%) of the 55 patients expired during the study period; nine of them had underlying conditions. Twelve different *emm* types were associated with these 13 patients.

DISCUSSION

The present study highlights the clinical features of iGAS disease and characteristics of GAS strains causing them among south Indian patients seen in a tertiary care center during a seven year period. Higher prevalence among neonates and elderly patients, presence of underlying conditions, and high diversity among GAS strains were the highlights of our findings. These are similar to the findings of Haggar et al [12] who recently documented important epidemiological differences in iGAS disease seen in India and western countries. Our findings assume significance in the context of scanty literature on iGAS in India.

High prevalence of iGAS disease among elderly patients and neonates is a unique feature of iGAS disease in southern India. Nearly two-thirds of cases were among patients above 51 years of age (42.1%) or neonates (21.1%) indicating a higher susceptibility of extreme age groups to invasive disease, probably because of lowered immune status. Such a distribution has been reported from other populations that are endemic to GAS infections [10]. Slight variation in age related incidence was found among North Indian isolates where the prevalence was found to decline with advancing age and very few cases were seen in the 35 – 64 year age group[12]. This difference is hard to explain although it may be related to the smaller sample size in the north Indian site of the study.

Presence of underlying disease in a large number of elderly patients (54.3%) shows that this is a major factor in the pathogenesis of iGAS among our elderly population. This has been stressed in the earlier study of Haggar et al [12] where malignancy and diabetes mellitus together accounted for 14 (45.2%) cases for which the nature of underlying disease was known. Similar results have also been reported by Steer et al [10] in Fijian population showing that this is a general trend in areas highly endemic for GAS infections. This needs to be considered while management and treatment protocols are put in place to control iGAS disease.

Analysis of clinical syndromes causing invasive disease showed that their epidemiology is significantly different from that of the western countries. Highest incidence was in patients with sepsis (22.2%) followed by meningitis ((15.8) and peritonitis (14%). Hagger et al [12] observed very low levels of super-antigen neutralizing activity in the sera of Indian patients showing that Indian patients are as much susceptible to invasive disease as their counterparts in the western countries. Yet there were only three cases of necrotizing fasciitis (NF) and no case of toxic shock syndrome (STSS) in our series. The low prevalence of such cases in an area where GAS infections and their sequelae are endemic is intriguing. Host-related factors especially underlying conditions appear to play important role in the pathogenesis of invasive disease in this population.

The present study also showed a wide variety of clinical disease associated with invasive disease as indicated by the isolation of GAS strains from sterile sites. Such a wide spectrum of diseases resulting in invasive disease appears to be typical of endemic situations and may be closely associated with high heterogeneity among *emm* types that circulate in this population [8,9,13]. Lack of cases of STSS and NF among our patients confirms that the epidemiology of iGAS disease in endemic regions is significantly different from that of industrialized countries.

Identification of 42 *emm* types in 57 isolates confirms a very high degree of heterogeneity among GAS isolates causing invasive disease in southern India. Four types namely 63, 74, 85 and 110 accounted for 12 (21.0%) of the 57 isolates. Another seven types accounted for 14 isolates (24.6%) while remaining 24 types accounted for one isolate each. A look at the type distribution among diverse clinical conditions (n = 42) showed no predominance of any individual type. This confirms that any GAS *emm* type can be involved in invasive disease. This is probably to be expected in an endemic area where a large number of types circulate in the community. A comparison with types reported by Haggar et al [12] showed that only eighteen of the 42 types identified in this study were seen in their series (n=32). High heterogeneity of *emm* types and lack of clonality among them make the prospects of a multivalent GAS vaccine very bleak in this population.

Reported literature of GAS invasive disease in India is scanty. Mathur et al [13] in a retrospective study described 225 (0.1%) GAS isolates from 2, 19,934 clinical samples over period of 5 years. Seven (35%) of the isolates from sterile body fluids were from 15 - 44 year old patients and all had underlying conditions. Three patients presented with toxic shock syndrome of which two had underlying systemic lupus erythematosus with nephritis. Among 205 soft tissue isolates, none had necrotizing fasciitis or any predisposing actors.

STSS which is a predominant feature of invasive GAS disease in western countries [4] is a very rare entity in the Indian population. To the best of our knowledge, there is only one report on STSS from India reported from Vellore in a patient with multisystem disease [14]. Serological and bacteriological evidence strongly suggested an underlying GAS infection.

In endemic situations, GAS infections may complicate into unexpected clinical conditions. An outbreak of an illness with fever, mono-, pauci- or polyarticular arthritis, and high antideoxyribonuclease B (ADNB) titers was reported in 11 patients in south India [15]. Blood culture grew Group A beta haemolytic streptococci in one patient. Most patients recovered completely, but one developed rheumatoid factor negative spondyloarthropathy. Monoarticular arthritis in several patients, the absence of carditis, and the presence of high ADNB titers without high anti-streptolysin O titers indicated that this was not acute rheumatic fever but post-streptococcal reactive arthritis.

CONCLUSIONS

Our findings confirm significant differences in the nature of iGAS disease seen in south India as compared to western literature. It also shows the need for constant monitoring of neonates and elderly patients with underlying conditions who tend to develop severe invasive disease than other age groups. We conclude that active surveillance of GAS infections both in the laboratory and clinical setting is necessary for the successful management of patients with iGAS disease in endemic areas.

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Conflicts of Interest: There are no conflicts of interest.

Table 1: Age - sex wise distribution of invasive GAS disease

Age group	Male	Female	Total	
			No	%
Neonate	8	4	12	21.1
>28d – 1 yr	1	2	3	5.3
2 - 10 yrs	1	1	2	3.5
21 – 35 yrs	6	4	10	17.5
36 – 50 yrs	4	2	6	10.5
51 – 65 yrs	11	4	15	26.3
>65 yrs	8	1	9	15.8
Total	39 (68.4%)	18 (31.6%)	57	100.0

Table 2: Clinical syndromes among patients with invasive GAS disease

Clinical syndrome	Frequency	%
Sepsis	13	22.8
Meningitis	9	15.8
Peritonitis	8	14.0
Cellulitis	5	8.8
Pneumonia	4	7.0
Necrotizing fasciitis	3	5.3
Umbilical	3	5.3
Arthritis	2	3.5
Puerperal sepsis/ Retained placenta	2	3.6
Empyema	1	1.8
Endocarditis/Pericarditis	1	1.8
Gangrene	1	1.8
Pleural effusion	1	1.8
Septic arthritis	1	1.8
Urogenital	1	1.8
Details not known	2	3.5
Total	57	100.0

Table 3: Underlying conditions among patients with invasive disease.

Underlying condition	Number	%
Malignancy	7	12.3
Diabetes mellitus	7	12.3
Lung disease	5	8.8
HIV/AIDS	3	5.3
Chronic liver disease	3	5.3
Skin abnormality	2	3.5
Autoimmune disease	1	1.8
End stage renal disease	1	1.8
Systemic lupus erythematosus	1	1.8
Alcoholism	1	1.8
No underlying disease	24	42.1
Not available	2	3.5
Total	57	100.0

Table 4: Age distribution among patients with and without underlying condition (n = 57)

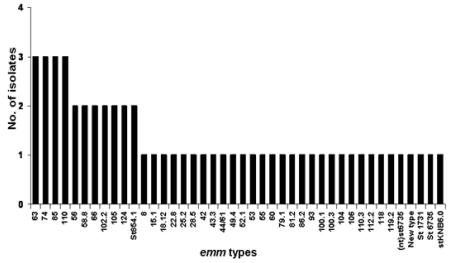
Age Group	Underlying Disease	
	YES	NO
Neonate	1	11
>28d - 1 yr	0	3
2 to 10 yrs	0	2
21 to 35 yrs	4	6
36 to 50 yrs	5	1
51 to 65 yrs	13	2
> 65 yrs	8	1
Total	31	26

Table 5: Distribution of 42 emm types in diverse clinical conditions

Clinical Condition	Number of *emm* types	*emm* types
Sepsis (14)	13	105, 55, 43.3, 85(n=2), 100.3, ntst6735, 66, stKNB, 6, 74, 53, 81.2, 110.3
Meningitis (7)	7	44, 60, 63, 66, 119.2, 74, 124
Peritonitis (8)	8	106, 104, 52.1, st854.1, 28.5, new type, 63, 25.2
Cellulitis (5)	4	110(n=2), 42, 18.12, 63
Pneumonia(4)	4	100.1, 102.2, 15.9, 49.4
Necrotizing fasciitis (3)	3	22.8, 118, 105
Umbilical Infection (3)	3	93, 8, 112.2

Numbers in parentheses indicate total number of isolates in each clinical condition

Fig 1: Distribution of 42 emm types among 57 GAS isolates



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