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Streptococcal disease complex

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Streptococci are microbials that cause diseases which are detrimental to health and economy worldwide, especially beta hemolytic streptococci group A (GABHS) whose late complications are rheumatic fever (RF), rheumatic heart disease (RHD) and acute glomerulonephritis. Diagnosis required reliable culture or rapid streptococcal antigen detection method along with rising antibodies.

Streptocci group B causes infection more commonly in pregnant women and their neonates. Streptococci group G are seen with increasing incidence as pathogens in normal and immunocompromised hosts. Streptococcus mutans are believed to be cariogenic. Streptococcal pneumoniae remain significant causes of respiratory, neurological infections and septicemia.

The National Streptococcal Reference Centre in Thailand, Faculty of Medicine, Chulalongkorn University, surveyed 1472 students from slum areas of Bangkok and found that 759 (51.2%) had positive throat cultures for B hemolytic streptococci. This was the highest incidence that had ever been reported in the country. The finding clearly indicated that streptococci still remained an important microorgamsm causing infections. Vaccines derived from M protein of GABHS has been under investigation. Mucopolysaccharide vaccines from streptococcal pnuemoniae should consist of serotypes that are prevalent in each locality so protective effect can be expected. This vaccine, though in use in many countries, is still not available in Thailand.

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จิริ รอดต้า, เสาวนีย์ จำเดิมเผด็จศึก. โรคซึ่งเกิดจากการติดเชื้อสเตรปโตคอคคัส. จุฬาลงกรณ์เวชสาร 1990 มีนาคม ; 34(3) : 169-176

เชื้อสเตรปโตคอคคัสเป็นจุลชีพซึ่งก่อให้เกิดโรคหลายชนิดเป็นผลเสียต่อสุขภาพและเศรษฐกิจของประชากรทั่วโลก โดยเฉพาะอย่างยิ่งสเตรปโตคอคคัสกรุ๊ฟเอ ซึ่งทำให้เกิดผลตามหลังคือ ไข้รูห์มาติก โรคหัวใจรูห์มาติกและไตอักเสบ การวินิจฉัยโรคต้องอาศัยห้องปฏิบัติการด้วยวิธีเพาะเชื้อ หรือตรวจหาแอนติเจนซึ่งให้ผลรวดเร็ว แอนติบอดีต่อเชื้อนั้นจะช่วยการวินิจฉัยเมื่อตรวจอย่างน้อย 2 ครั้ง และมีไตเตอร์เพิ่มขึ้น การรักษาคือเพนนิซิลินเมื่อติดเชื้อหรือป้องกันด้วยเพนนิซิลิน เมื่อมีไข้รูห์มาติกหรือโรคหัวใจรูห์มาติก สเตรปโตคอคคัสกลุ่ม บี มีความสำคัญในหญิงมีครรภ์และเด็กแรกเกิด ส่วนกลุ่ม จี พบว่าเป็นทั้งจุลชีพปกติหรือก่อโรคทั้งในคนปกติและคนภูมิคุ้มกันพร่อง กลุ่มอื่น ๆ เช่น สเตรปโตคอคคัสมิวแตน (S.mutans) พบว่าอาจทำให้เกิดฟันผุ สเตรปโตคอคคัสนิวโมนิอีเป็นสาเหตุของการติดเชื้อในระบบต่าง ๆ ได้มาก โดยเฉพาะระบบทางเดินหายใจ ระบบประสาทและการติดเชื้อในกระแสโลหิต

จากการสำรวจของศูนย์สเตรปโตคอคคัส คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย พบว่าเด็กนักเรียนจำนวน 1,472 คน มีเชื้อสเตรปโตคอคคัสกลุ่มต่าง ๆ ถึง 759 คน คิดเป็นร้อยละ 51.2 ซึ่งมากกว่ารายงานทั่วไปและรายงานจากการศึกษาอื่น ๆ ในประเทศไทยมาก จึงเห็นได้ชัดว่าจุลชีพนี้ยังเป็นปัญหาของประเทศไทยตั้งแต่อดีตถึงปัจจุบัน ควรได้รับการดูแลให้ถูกต้อง

วัคซีนซึ่งทำจาก M โปรตีนของเชื้อสเตรปโตคอคคัสกรุ๊ฟ เอ อยู่ระหว่างการศึกษาวิจัย ส่วนวัคซีนป้องกันเชื้อสเตรปนิวโมนิอีนั้นต้องประกอบด้วยซีโรทัยป์ที่พบบ่อยในแต่ละท้องถิ่นจึงจะได้ผล ในประเทศไทยยังไม่มีการนำวัคซีนนี้เข้ามาใช้

Streptococcal diseases represent a world-wide health and economic problem. Available data on the incidence of streptococcal infections indicate that they are one of the most frequent bacterial diseases in the temperate zone and are common in tropical and subtropical areas.[1]

Human pathogenic Streptococci belong to a large number of species with diverse biological properties. They produce diseases with a variety of clinical symptoms. These pathogens are ubiguitous and wide spread in all parts of the world. This situation is speculated to last over many decades to come. It stimulates and justifies the fundamental and applied researches with the goal to further improve health services in diagnosing, treating and preventing streptococcal infections.

The purpose of this paper is to review the importance of pathogenic streptococci.

B hemolytic streptococci (BHS)

Group A BHS

The most common streptococcal infection is tonsillopharyngitis caused by group A, beta hemolytic streptococci (GAS) which may be complicated by late sequele of rheumatic fever, rheumatic heart disease (RF/RHD) and acute glomerulonephritis (AGN) if no treated early and properly. Skin infection is associated with AGN but not RF/RHD.

At its General Assembly Meeting held in 1983, the World Health Organization passed a resolution of paramount importance for global control plans on the streptococcal disease complex. The resolution urges WHO member countries to pay particular attention to the prevention and control of cardiovascular diseases, emphasizing coronary heart disease, hypertension and RF/RHD. A National control programme on RF/RHD was shown to be feasible.[2] It is already being carried out in a number of countries. The programme includes health control projects, organizing of national symposia, training courses and other activities in 16 countries. The programme is assisted by WHO.

In Thailand, the project has been launched in 1985 at two provinces, Bangkok and Nakorn Rachasrima as a pilot project for RF/RHD registry, new case findings and secondary prophylaxis. The aim is to cover as many provinces as possible, if this health care delivery system for the periphery proved successful. It was found that the success rate of secondary prophylaxis of RF/RHD was 77.32%.[3]

However, from the recent survey by the National Streptococcal Reference Centre in Thailand (NSRCT) in November 1988, it was found that in school children from slum areas in Bangkok, The throat swab culture by direct plating on sheep blood agar with supplement showed 51.2% prevalence rate of B hemolytic streptococci. (Table I) Only one case of old RHD was found in 1600 children examined.

Table 1. The result of BHS from throat swab in 1472 school children.

Number of BHS	Percent of Lancefield group				
	A	B	C	G	others
759	36.8	12.2	6.56	44.1	.5

The incidence of RF has dramatically declined in the countries of the moderate zone, accounting for some 1 or 2 cases per 100,000 per year, or even less. It is unlikely that RF/RHD will disappear or be eradicated as long as group A streptococci circulate in the population. Recently, this has been documented by a sudden reappearance of RF in the United States. Outbreaks have been recorded in various parts of the country in the middle class population. In one place, for example, 140 cases were registered over a short period of time. Streptococci type M 18 was involved. It is presumed that many factors were responsible for the high incidence.[4,5]

In recent decades, data on the magnitude of RF/RHD problem have become available in an increasing number of countries belonging to the hot climatic areas. RF is frequently encountered and RHD is one of the most common heart diseases.[6]

Primary prophylaxis of rheumatic fever is an efficient treatment of group A streptococcal infection of the upper respiratory tract. Secondary prophylaxis of rheumatic fever is a longterm prevention of group A infection by penicillin in individuals who have already had RF/RHD.

At the present, the only measure applicable for the control of group A streptococcal disease is administration of penicillin. It is used not only for therapy but also for prophylaxis. This mode of control is not considered to be the final solution of the problem for a number of reasons, that is, the use of penicillin over a long period of time may have deleterious effects in some individuals. Moreover, it cannot be guaranteed that the group A streptococci will not gradually develop resistance to the drug.

The diagnosis of upper respiratory tract infections caused by group A streptococci, the most frequent streptococcal pathogens in man, based only on clinical symptoms is highly inaccurate. Microbiological confirmation of clinical diagnosis is essential, in ensuring accurate documentation of group A streptococcal infections. This involves isolation or direct identification of group A streptococci, demonstration of rising antibody titre against streptococcal antigens or toxins. Adequate laboratory facilities are vital to RF/RHD diagnosis and prevention programmes.[7] (Table 1 and Table 2)

Serological examination for streptococcal antibodies of paramount importance in this regard because, at the start of a RF/RHD attack, the group A streptococci are frequently no longer present in the upper respiratory tract. While a single elevated titre may be useful in documenting a previous streptococcal infection, it is recommended that acute and convalescent serum samples, taken at the onset of the rheumatic fever attack and 3-4 weeks later, should be examined simultaneously. Levels of antistreptolysin O and, if possible, antideoxyribonuclease B, should be determined in all instances. Tests for antihyaluronidase, antistreptokinase and antidiphosphopyridine dinucleotidase may also be carried out. While condiserable attention has been given to a commercially available agglutination test for simulatneous determination of several antibodies, a recent WHO study and other published reports have indicated that the test is not consistently reliable and cannot be recommended at this time.[8]

Measurement of levels of antibody to group A streptococcal polysaccharide, a somatic antigen, may also be helpful in determining previous infection. However, more data are needed on the biological significance of the test before its diagnostic and prognostic value can be assessed.[9]

The efficiency of continuous secondary penicillin prophylaxis for prevention of rheumatic fever should be confirmed periodically when possible.[10] Becteriological examination of throat swabs can confirm the presence or absence of GAS.

At present, however, it is difficult to perform microbiological diagnosis of group A infection on a large scale in the periphery level because this involves the use of laboratory procedures.

Table 2.

Minimum Reguirements for Microbiological Examination of Streptococcal Throat and Skin Infections

Microbiological Examination	Clinical Patterns				
	Carriership	Pharyngitis Impetigo	RF	AGN	RHD
Bacteriological : culture method,	(*) +		+	+	
non-culture group A direct test,		+	−	−	−
serological grouping			+	+	+
group A typing			+	+	
Serological : ASO			+	+	+
ADNase B			+	+	+
Anti CHO-A			+	+	+
Antimyocardial			+	+	+

(*) If not indicated, the examinations should only be performed when required for clinical or epidemiological reasons

Table 3. Identification of Group A Streptococci in Carriers by Culture Method (CM) and Direct CO-Agglutination Test (COA).

CM Results			COA Results		Accuracy			
Streptococci isolated	Total no	Colony 1) count	+	−	Agreement	Confidence limit 95%		
GAS	32	100	22	10	69	50	-	82
	87	100	32	55	37	27	-	47
Streptococci other than GAS	178	nd	4	174	98	95	-	99
Negative for streptococci	846	na	19	827	98	97	-	99

1) colonies per plate
nd : not determined
na : not applicable

A rapid non-culture diagnostic technique has been elaborated for the identification of group A streptococci in clinical specimens taken from patients with pharyngitis. The diagnostic testing is done by a co-agglutination reaction (COA) between the reagent (immunoglobulin against group A polysaccharide bound to S. aureus) and HND2 extract of the clinical specimen (swab) prepared under controlled conditions at 100°C. It takes 3 minutes to complete the test and to read the result.

This technique for rapid identification of group A streptococci (GAS) has been evaluated in a WHO-coordinated international study.[11] The direct test, (Table 3) as compared with the conventional culture method, was shown to be sufficiently sensitive and highly specific when used in the diagnosis of streptococcal pharyngitis. Another technique by latex agglutination test is at present under evaluation.[12]

The justification for the research towards the vaccine against group A streptococci is as follows:-

1) The streptococcal pharynigitis may be asymptomatic so that the person is not treated with penicillin with the complications of RF/RHD

2) If the vaccine is made available, it could replace the need for penicillin (as) secondary prophylaxis.

The M protein of GAS is the factor of virulence, it is a type specific substance, (and it) protects GAS against phagocytosis. After infection, the type-specific antibody to M protien develops which provides immunity.

The chemical composition of M protien of several types was studies (Table 4) The epitopes located in the molecule were identified, and the cross reactive components with human heart tissue have been described. Finally, some epitopes have been made synthetically or had been isolated from the native material, deprived from the fragments deleterious to human's heart. They are immunogenic leading to the development of protective antibody.[13]

Although a substantial progress has been made, there are still many factors to be learned before the vaccine can be administered to man. For example, the safety of the vaccine, a sufficient level of antibody with protective property a long lasting antibody response, the identification of individuals who should be vaccinated (for example the theumatics, children with repeated streptococcal infection). It shoud also be clarified as to which are the prevailing types of GAS in various parts of the world and which are the types causing pharyngitis that are frequently followed by rheumatic fever.

Table 4. Typing Systems for Group A Streptococci.

M typing	T typing	SOF typing
	Identify	
M type	T pattern	M (SOF) type
	Differentiate between	

M types 1 to 71 (72 to 81)*	**T patterns (include one or more M types) (72 to 81)***	**M(SOF) type (Identical with types)**
Numbers not used :	1.....1.68	2,4,9,11,13,22,25,28,48
7,10,16,20,21,35,64	3/13/B	
	3264.....3,13,33,39,41,43,52,53, 56,67,71,72,73,77	49,58,59,60,61, 62,63,66,68,73,75
Partial antigenic	4/28.....4,24,26,28,29,46,48,60,63	76,77,78,79,81
relationship in types :	5/12/27.....5,11,12,27,44,61,62,66,70,76,78	
13 + 48	6.....6	
2 + 48	8/25/lmp. 19..2,8,25,31,55,57,58,59,65,75,79	
3 + 12	9.....9,74	
33 + 41 + 43 + 52	14/49.....14,49,51,80	
	15/23/47.....15,17,19,23,30,47,54,70	
	18.....18	
	22.....22	
	N.T.....81	

* Provisional M types

Group B BHS

The virulence factor as well as the type specific substance in the group B streptococci is the capsular polysaccharide. In turn, the immunity is type-specific. The protective IgG antibody is directed to the capsular polysaccharide. Out of the group B types Ia, Ib, II, III, Iv and V, type III is the most common type causing two thirds of neonatal and infant infections.[14,15]

Other pathogenic streptococci

Pathogenic streptococci causing bacterial endocarditis as well as other clinical patterns include various species, such as S. Sanguis, S. bovis, and S. milleri. A new level of information about their biological properties have been obtained. For example, an M protein has been found in group G streptococci. High degree of cross-reactivity of this M protein with the M protein of type 6 group A streptococcus has been demonstrated. The present knowledge enables taxonomic classification to be made in routine diagnostic practice which is the prerequisite for an adequate treatment.[16]

Group G BHS is found more frequently in many parts of the world causing a variety of clinical presentations from tonsillitis, sepsis, acute food poisoning, skin infection, to osteomyelitis in normal and immunocompromised hosts.[17,18]

The National Streptococcal Reference Centre in Thailand had found that the specimens received in 1988 also showed this trend. Group G streptococci were found in blood, pus and other sources as shown in table 5.

Table 5. Source of specimens for streptococci group A & group G.

Serogroup of BHS	Total	Source of specimens					
		Blood	Pus	Throat	Cervix	Body fluids	Other
A	129	10	92	16	2	3	6
G	77	12	28	25	5	2	5

The consistent presence of S. sanguis and S. mutans in dental plaque and the cariogenicity of S. mutans in experimental animals indicate the potential association of these streptococci with human dental caries.[19] Research was launched into the cellular components and extracellular products of both microbes with the aim to elaborate a vaccine for active immunization against dental caries in man. Conclusive data were obtained on the antigenic components and on their role in model experimental caries in animals and men.

Streptococcal pneumoniae

Infections caused by S. pneumoniae occur under various clinical patterns. The serious life threatening presentations are pneumonia, meningitis bacteremia, and primary peritonitis. Individuals at risk include those with functional or anatomical asplenia, nephrotic syndrome, those about to undergo cytoreduction therapy for Hodgkin's disease, HIV infection and the elderly.[20,22]

The S. pneumoniac vaccine is the only one available so far, and is prepared against infections by path ogens belonging to the genus Streptoccocci and at present, only the pneumococci.

The prerequisite for its elaboration was the recognition of the type-specific capsular polysaccharide which is the virulence factor, it is called specific soluble substance (SSS). The antibodies to this polysacchride are responsible for the immunity and is type specific.

The proposal for the composition of the vaccine, which is polyvalent, was made possible by monitoring and mapping of the prevailing types responsible for most of the serious pneumococcal diseases in various parts of the world[22] Until now, 83 capsular types have been indentified.[23]

Conclusion

Streptococci are important bacterial infection in man, causing a variety of clinical presentations, GAS posted a unique problem due to its late complications namely RF/RHD and AGN. These can be prevented with penicillin is effective in RF/RHD but is not the final answer to the problem.
to the problem.

More information on the organisms'structure and host's response has led to better laboratory diagnostic methods and future vaccine development.

The health and economic importance of streptococcal infections in all parts of the world fully justifies the work at elaborating better technology for diagnosis, therapy and control of these diseases.

The global approach to this problem is realistic for bringing positive results in the near future.

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