Mini Review

Rheumatic Heart Disease (RHD) Prevention and Control in North India: Addressing the Challenges

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Abstract

Rheumatic Heart disease (RHD) is one of the major causes of morbidity and mortality especially among 5-15-year-old children in developing countries like India. Globally, 15.6 million people suffer from RHD each year, and in India 600,000 children of less than 15 years suffer from this disease. Although incidence of RHD has come down with improvement in living conditions, but sporadic emergence in developed countries and continued persistence in developing countries is still an issue. RHD is preventable, yet there are many challenges which need to be addressed. In this review we have discussed key challenges which are hindering the efforts for prevention and control of this neglected disease.

INTRODUCTION

Rheumatic heart disease (RHD) caused by Group A Streptococcus (GAS) infection, is the leading cause of mortality in cardiovascular disease group both in children and youth. Infact Streptococcus is the chain which links throat to heart valve [1]. Globally, the prevalence of RHD is approximately 15.6 million cases with 282,000 new cases and 233,000 deaths each year. In India, approximately 600,000 children less than 15 years of age suffer from RHD. However, due to the rise in socio-economic status in western countries, the incidence rate of RHD cases has come down, yet frequent sporadic cases are observed. On the other hand, high incidence and prevalence in Asian and African countries with high morbidity and mortality remains a challenge [2-4].

High incidence of RHD is attributed to GAS virulence factors, host genetic susceptibility, environmental factors and exaggerated immune response. Hence, it is the need of the hour that the challenges, which determine the higher burden of RHD in developing countries especially in India, should be addressed. Herein, we highlight a string of issues which impair the efforts to reduce the RHD burden by critical review of available information from the regions of North India.

Epidemiological challenges

Streptococcus pyogenes or Group a streptococcus is one of the most enigmatic bacteria capable of causing an array of diseases in humans and RHD is one of them. Disease burden of GAS is high in lower, middle and high income countries with more than 600 million cases worldwide [5]. Epidemiological distribution of GAS and its associated diseases pose a significant threat due to less understood mechanism of pathogenesis.

Several epidemiological investigations, keeping in view the prevention and control, have been done at our centre in the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India since many decades. Nandi et al. [6], conducted a survey in school children in peri-urban slum area of Chandigarh (India) where incidence of GAS sore throat was found to be 0.95 episodes per child per year. A clinical score card system was developed for early diagnosis of GAS infections. We observed that clinical score card along with the culture result may help the clinician to narrow down the patient population for antibiotic treatment; this will further help in ruling out the viral etiology of pharyngitis. Our observation is also in accordance with Infectious Disease Society of America (IDSA) [7]. Many epidemiological studies were conducted over a period of about thirty years in rural areas of Raipur Rani Block in Haryana, India [8-10] and in at Rupnagar district in Punjab [11]. Enormous efforts have been made to understand the epidemiological aspect of the streptococcal infections, and over the period various policies were also drafted to control RHD.

A registry was started to enrol all the RHD patients residing in Rupnagar district near Chandigarh (50 km from Chandigarh). Nearly 813 cases of RF/RHD were registered from 2002 to
2009. Out of the 813 cases, 610 cases were RHD indicating the high prevalence of disease in the state [11]. Since 2008, under the Rashtriya Bal Swasthya Karakarm (RBSK) or National Child Care Programme as many as 3456 children having congenital heart disease and rheumatic heart disease have been referred to PGIMER, Chandigarh, India and other tertiary hospitals for treatment where 2129 children have been operated [12].

The challenge which still exists as far as epidemiology is concerned is the huge strain heterogeneity which exists in Indian GAS strains in comparison to strains from western regions. S. pyogenes has a range of virulence factors in its arsenal, of which M protein in one of the most dominant antigen. The M-protein is coded by emm gene which has many subtypes, and a geographical area can have various GAS strains with different emm types. We have reported many epidemiological studies where emm typing of GAS strains was done and each of these studies from Chandigarh and its nearby areas indicated that our most prevalent types are quite different from the ones in other countries [13-16]. Our two main studies too identified 37 and 27 different emm types respectively indicating huge heterogeneity among the GAS isolates [15,16]. These prevalent emm types in north India were found to be different when compared to south India [17].

Continuous emergence of new strains is also a burning issue which needs an attention. In North India, emm 1, which is prevalent all over the world, was rare; instead a highly invasive emm1-2 strain prevalent in Chandigarh, India [18]. emm 1-2 might have evolutionarily emerged from emm1. Therefore, designing preventive strategies based on vaccine would be an uphill task with such wide and varied distribution of GAS strains.

Socio-economic challenges

There are plethora of evidences which support the surge and decline of S. pyogenes infection depending upon the season, nutritional status, and mode of cooking fuel used. Lamagni et al. [19], noted change in lesser disease incidence in the autumn and then increasing in December through April. Similar study from our laboratory also reported incidence of sore throat correlated with age, season and also with living conditions of children. It was observed that incidence was higher in 11-year-olds, during winter and rainy season and among children who lived in the houses where there were no separate kitchen [6].

Epidemiological studies have shown the occurrence of S. pyogenes infection with higher predilection towards men than women. On the contrary, the post streptococcal autoimmune infection such as rheumatic fever and rheumatic heart disease are higher in women than in men as observed with respect to other autoimmune diseases also. In a report submitted to Indian Council of Medical Research (ICMR) it has been mentioned that although prevalence of RHD among boys and girls in school surveys was same however higher number of RHD cases were registered in females of above 20 years of age [8]. Studies from India highlight the harsh reality of significant gender bias toward the female sex. It was found that the “female” gender was the major factor responsible for not receiving the medical treatment, which may be due personal and social discriminatory practices. Other factors which aggravated the gender bias were lower socioeconomic class and the cost of surgery [20-22]. Gender bias has also been documented in nutrition as well as in vaccination wherein male children were preferentially vaccinated and given nutritious food than the female child [23]. A recent study in the area adjacent to Chandigarh region also highlights the gender bias in cardio vascular health in spite having the option of free treatment [24].

Hence, it can be said that although improvement of living conditions and awareness might have largely decreased the prevalence of RHD in urban settings however, poor living condition, socio-economic bias in the rural areas of Chandigarh increases the risk of GAS infection, ultimately leading to RHD.

Biological challenges

Host pathogen interactions provide an insight in comprehending the pathogenesis of the disease. However, in case of RHD the exact pathogenesis remains elusive which creates a gap between the diagnosis, treatment, prevention and control. One of the biological challenges is that no biomarker is clinically accepted till date for diagnosis of RHD in any of its stages (pharyngitis, ARF and RHD). In Chandigarh we did identify a HLA-DRB1 *14 as a genetic susceptible marker in RHD patients [25]. We had also attempted to identify the stage specific marker including by product of collagen metabolism (PCIP), anti-PARF (Peptide Associated with Rheumatic Fever) antibody and serum cytokines level [26]. We found the high level of anti- PARF antibody in serum of ARF patient but these were low in pharyngitis and RHD patients. Whereas, by product of collagen metabolism, C-terminal of type I collagen, was high in RHD compared to other groups. However, serum cytokines other than IL- 6 did not show any significant difference among disease and healthy population. Number of studies has identified various molecules such as fibroblast growth factor-21 [27], IL-10 and endothelin -1 [26], plasma gelsolin [29] any more but these have failed to get wide acceptance. Thus, markers which determine the advancement of ARF to RHD or pharyngitis to ARF remain obscure. This affects the development of prevention and treatment strategies, which increases the economic burden due to the need for chronic medication and mitral valve replacement surgery.

In addition, emergence of antibiotic resistant strains over a period of time is another challenge. The non adherence to antibiotics and positive selective pressure on prevalent GAS types and subtypes may result in the emergence of drug resistance as seen in similar streptococci species [30]. Our first report on antibiotic resistance status of Indian GAS strains antibiotic resistance confirmed that antibiotic resistance strains are prevalent in North Indian community [16]. However, most of the GAS strains are still sensitive to penicillin but emergence of antibiotic resistant strains remains an imminent threat. Our Study in Chandigarh region also highlighted that penicillin sensitivity (99%) in GAS strains. Besides, the GAS were resistant to tetracycline (25.5%), 7.8% to azithromycin, 4.9% to clarithromycin and 3.9% to both chloramphenicol and amikacin. This study has also shed light on resistant pattern to dinamycin, ampicillin, co-trimoxazole and gentamicin, wherein all the GAS strains were resistant to these antibiotics. Contrastingly group C and Group G streptococci were sensitive to these antibiotics [16]. Variations in antibiotic sensitivity towards the site and disease
specific isolates were also observed. In clinical settings like India where antibiotic awareness is minimal in rural areas, it will be justified to view antibiotic policy and its awareness as major challenge in war against RHD. Limited information is available on antibiotic resistance, thus continuous monitoring regarding the matter is required to control RHD.

To lessen the burden of disease, vaccine against group A streptococcus is needed, however it is still a dream to be realised. Few vaccines based on M protein [6, 26 and 30 valent] [31-33], carbohydrate antigen [34], serum opacity factor [35], fibronectin binding protein [36], streptococcal pyrogenic exotoxin A [37] etc. are at various stages of development. Various factors such as prevalence of emm types in geographical area and also the lack of consensus for a pathway against which the vaccine shall be developed are detrimental to vaccine development [38], WHO report accurately terms GAS vaccines as impeded vaccine in spite of some major breakthrough [39).

Greater challenge for vaccine development is the GAS strain heterogeneity. As discussed before, since our prevalent emm types are quite different from the other countries, hence multivalent vaccine, which is currently under research, may not be suitable for Indian subcontinent. The approach for the development of indigenous vaccine needs to be explored further.

We have two reports on vaccine development, where C terminal conserved region is targeted as a vaccine candidate [40, 41]. As far as N terminal multivalent vaccine is concerned, based on strain heterogeneity, different emm types needs to be selected. The prevalence of emm types in particular region and variation in emm gene will determine the vaccine design and efficacy; other issues include safety concerns, and minimal development of combination antigen vaccines (WHO report). Thus, it is imperative to understand the enigmatic pathogenesis of RHD for diagnosis, treatment and prevention.

CONCLUSIONS

Although, RHD remains a neglected disease nationally however, a lot has been done in the rural settings of north Indian community for control of the disease. As quoted by Ramakrishna S [42] that RHD is “buried alive”, and it requires many steps for the RHD control such as social awareness, free distribution of antibiotics and annual check up of school going children. There is an urgent need to keep a check on GAS-RF-RHD nexus but continuous emergence of strains, antibiotic resistance, lack of diagnostic/susceptibility makers and vaccine development are still huge challenges which need to be tackled. However, in Chandigarh and in its neighbouring districts, we are conducting regular school check-up and maintaining registry on RHD and providing RHD prevention and control services to save the precious life of children and young adults.

REFERENCES


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