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Rheumatic Fever and Rheumatic Heart Disease: A Review on Current Diagnosis Methods and Challenges

Vandana[1, 2*], Geeta Singh[2], Ashok Kumar[1]
[1]CSIR-Institute of Genomics and Integrative Biology, Mall Road, Delhi-110007, India
[2]Departent of Biomedical Engineering, DCRUST, Murthal, Sonepat-131039, India

Abstract: The rheumatic heart disease (RHD) is beleived as a major menance in developing countries. There are many diagnostic methods available for detection of RHD. But these methods have several disadvantages like in term of sensitivity, selectivity, cost, so it is very important to develop a fast, sensitive, cheap device, which can easily available for RHD diagnosis. The major challenge is to find the pathophysiology of RHD, which is still unclear. Without understanding of pahophysiology it is not easy to control any disease. Evidences used in this review shows that molecular mimicry between *S. pyogenes* and human cardiac tissue is responsible for RHD. This review summerized the studies available for understanding pathophysiology of RHD and present available methods for detection of RHD and considerations of future prospectus for RHD diagnosis.

Keywords: **Pharyngitis; Rheumatic fever; Rheumatic heart disease; *Streptococcus pyogenes*.**

Introduction

Rheumatic heart disease (RHD) is defined as the impairment or any harm to heart valves and heart muscles which originate due to repeated instalment of acute rheumatic fever. Acute rheumatic fever is a resistant of body to group A Streptococcus (GAS) infection. Untreated GAS infection between 5-15 years results in ARF [1]. ARF mainly impact on central nervous system, heart, joints, skin, and brain. Symptoms of Rheumatic fever depend on type and severity of disease and the infected part of body. In human group A streptococcus (GAS) is an organism that results in a wide range of infections. Manifestations of disease can result in pneumonia, bacteraemia, necrotizing fasciitis, upper respiratory tract infections, skin and soft tissue Infections, and streptococcal toxic shock syndrome. In developing countries RHD is main cause of cardiac disease. Mitral valve is most commonly involved valve usually in 65-70% patients and about 25% patients are suffered from aortic valve disease, which further results in permanent heart damage or heart attack [2, 3]. Each year, about 233,000 deaths referable to RHD [4-6]. Socioeconomics and environmental constituents like overcrowding, poverty, and malnutrition play a big part in spread of RF [7, 8]. This review highlights the subsisting methods available for confirmation and diagnosis of RHD.

Epidemiology

In developed nations, the cases of GAS infections turn down [9, 10], this is because of accessibility of antibodies [11] and also due to bettered social and economic status. But it is still major problem in developing countries. There is a high frequency of GAS infection occurrence in children [12]. Every year about 233,000 death and nearly 282,000 cases occur. In developing nations, around 20 million persons are affected by ARF and RHD [13]. This is due to socioeconomic circumstances, deficiency of hygiene, excessive crowding in these countries [14]. Malnutrition results in decrease in immune response, overcrowding results in repeated attack of RF and due to deficiency of hygiene GAS tenacity will be increased in environment. In developed countries the number of cases of ARF and RHD has reduced because of accessibility and use of antibiotics for treatment of GAS infections and improvements in aspects of primary treatment. About 6-11/1000 school children are affected by RHD in India [5].

Pathogenesis

RHD is an outcome of unprocessed GAS infection. Kaplan in 1960 introduced the concept of participation of autoimmune reactions in pathologic process of RF [15, 16]. When reviewing all data define pathogenesis *S. pyogenes*, it is concluded that RHD can result from direct infection i.e through GAS, due to streptococcal toxin and also due to antigenic mimicry. After introduction of GAS infection, body produced antibody against pathogen. In pathologic process of rheumatic heart disease T lymphocytes play a significant part [17]. M types of group A streptococci have rheumatogenic potential. These features raise the potential of the bacteria to stick to tissue, and also their potential to

protest phagocytosis in the human body. MHC class II antigens is chiefly used by extracellular antigens to trigger immune response [18]. RHD results after introduction of throat infection by *S. pyogenes* in unprotected persons due to cross reactivity between human tissue proteins chiefly heart tissue proteins. The pathogenic mechanism of Rheumatic Fever is shown in figure 1 below

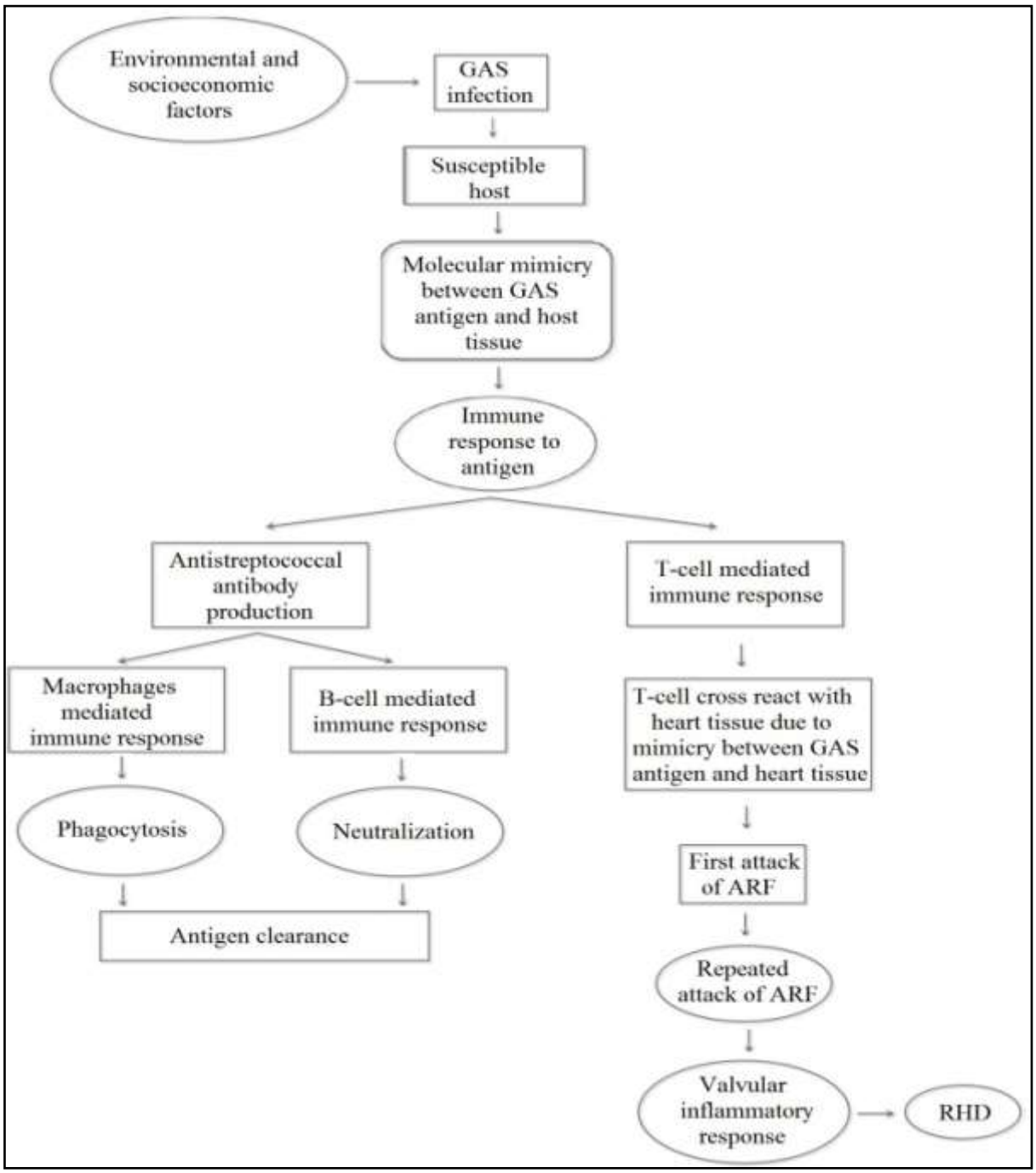

Fig. 1. Mechanism of pathology of RF.

DIAGNOSIS

In 1944, Dr T. Duckett Jones' introduced criteria for diagnosis of RF. According to this criteria the characteristics of RF were separated into major and minor manifestations based on particularity of manifestations. The American Heart Association (AHA) and the World Health Organization (WHO) review and modify the diagnosis criteria for RF expressed by Dr. T. Duckett Jones [19]. It consists major and minor manifestations which are given below in table 1.

Table 1. Jones criteria for RHD diagnoses (1992)

Major manifestations	Minor manifestations
Carditis	Fever
Polyarthritis	Mono arthritis
Chorea	prolonged PR interval ECG (electrocardiogram)
Erythema marginatum	Leukocytosis
Subcutaneous nodules	Previous episode of rheumatic fever

Presence of RF is defined if any two major or one major and two minor manifestations with an evidence for recent GAS infection. There are many diagnostic methods available which are given below.

a) The role of microbiology laboratory

For the exact determination of GAS microbiology play an important role, which require isolation and identification of GAS, which can help in prevention of RF. The patient suspected with infection of upper respiratory tract should be examine with throat swab. This swab sample should be cultured on blood agar plate [20]. 11% patients show Positive throat culture for GAS infection during ARF period [21]. Than rapid antigen detection test should be done. It is sensitive and specific and early treatment can be done with this technique [22]. Antistreptococcal antibody tests are important for GAS identification. Antistreptolysin O and antideoxyribonuclease B are commonly used antibody assay for GAS confirmation [23]. But this test is not much suitable for GAS confirmation due to less reproducible and less standardized.

b) The Role of molecular techniques

Due to specificity for detection of infectious disease molecular techniques are very important. PCR (polymerase-chain reaction) is one of the most sensitive and specific molecular technique which allow early diagnosis of RHD. The pathogen which cannot grow in culture can directly diagnose with help of PCR technique. For complete diagnosis of RHD PCR takes about 60 minutes in our laboratory [24].

c) Auscultation

In 1970, WHO acknowledge the importance of detection of RHD in it's previous stage. In 1984 WHO induce it's first plan for RHD diagnosis. With the help of auscultation about 1.4 million children were tested from 16 different countries. About 3,000 children were detected with former unknown RHD [25]. Due to easily availability of echocardiography and low sensitivity of auscultation it is now not commonly in use [26, 27]. Auscultation is cost effective, easy, fast method and it can easily performed by doctors.

d) Echocardiography

Due to development and easily accessible of electrocardiography, it is easy to detect RHD. From recent studies performed on school-children shows that preponderance of RHD with the help of echocardiography is much more sensible than clinical judgement. The main advantage of echocardiography is that it can detect minor changes and so useful in diagnose disease. Echocardiography is very sensible if any valve abnormality is present. Echocardiography has high sensitivity but less specificity so it can results in false positive rate. False positive rates results in unnecessary treatment with secondary prophylaxis which further produce harm in patient's body and also not cost effective. So it is necessary that echocardiography should carefully perform to avoid false positive rates [28, 29]. Echocardiography is more sensible than previous but it's cost is high and require trained physician.

e) Auscultation plus selective echocardiography

With the development of echocardiography, the children with cardiac murmur on auscultation, farther complied with echocardiography for RHD conformation. If physician perform auscultation alone than it is less sensible [27]. The echocardiography plus auscultation increase specificity and sensitivity and eliminate false positive results.

f) Future diagnosis by biosensor

The early diagnosis of RHD is very significant both for patient life and also saving cost and time. The methods which are available today are based on tests performed in clinical laboratories which is very time consuming and less sensible. Therefore a sensitive and fast technology is required for early detection of RHD. The biosensor technique is very sensitive, fast and cheap method which can help in early diagnosis and decrease the time consumption in diagnosis and provide better care for health [30]. According to IUPAC, a biosensor is defined as a self-containing integrated device, capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element which is in contact with a transduction element [31].

Bioreceptors also called biorecognition element like enzyme, nucleic acids, an antibody, has a potentiality to recognize any analyte. The transducer convert the interaction of analyte and biorecognition element into a noticeable signal. Quantitative analysis is accomplished if the strength of signal is proportional to analyte's concentration [32]. The general block diagram of biosensor is shown in fig. 2.

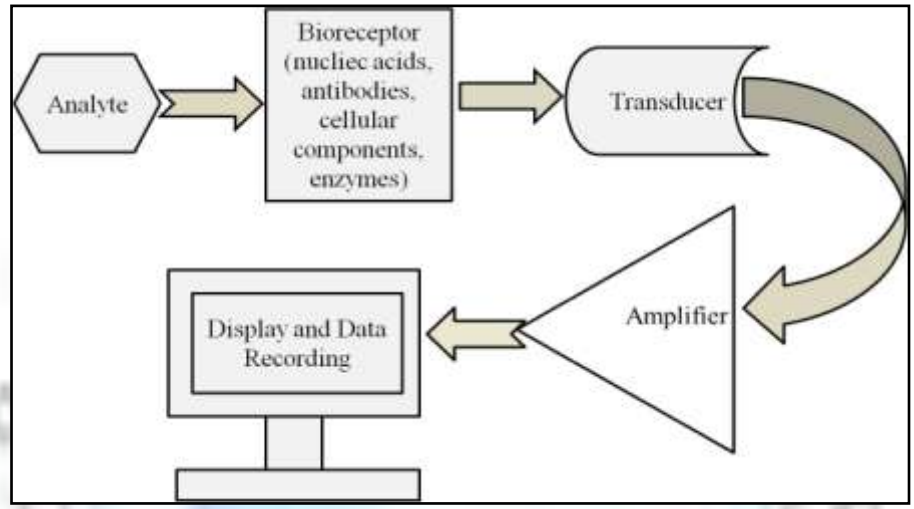

Fig. 2. Generalized block diagram of Biosensor detection principle.

In recent years development of DNA biosensor has development of DNA biosensors and DNA microarrays has increased. For detection of hybridized DNA, DNA-binding drugs etc electrochemical biosensors are majorly utilized. Screen-printing technology are used for the production of electrodes to develop fast, cheap and disposable biosensor [33]. With the development of Biosensor technique, a non-invasive procedure it is easy to diagnose RHD. It provides sensitivity and specificity and retrospective diagnosis. When comparing the biosensor technique with current available methods, which are time-consuming, and high cost, this technique possess specificity, cost efficiency, speed, and ease of use. By varying the material used for sensing integrates into the sensor may increase the area of application into diagnosis of infectious diseases. For detection of RHD electrochemical biosensor have great importance. These biosensors used immobilized probe as recognition element that binds to specific target molecule. Change at the surface which shows the binding of target to the probe in the solution is characterized by change in current or in voltage. The main advantages in the use of electrochemical biosensors are their sensitivity, selectivity and reliability. The main challenge is the disturbances produced on sensor surface due to pH changes and ionic strength. The direct detection of disease without sample preparation is major challenge.

The comprehensive analysis of all methods are given below in table 2.

S. No.	Techniques	Advantages	Limitations	References
1	Diagnosis of GAS infection with throat swab	Cheap method and accessibility in developing countries	Low sensitivity and time consuming	[20]
2	Streptococcal Antibiotic Tests	Useful for the patients with nonsuppurative complication of GAS infection	Less standardized and less reproducible	[22]
3	Rapid Strep Test	Both sensitive and specific and early treatment can done because it takes very	More expensive than culture method	[23]

		small time		
4	PCR based diagnosis	More specific and sensitive, allow early diagnosis	Time consuming and large process and require trained professionals	[24]
5	Auscultation	Cost effective	Less sensitive	[25]
6	Auscultation + Echocardiography	More specific and sensible	High cost, so not easily accessible in developing countries	[27]
7	Echocardiography	More sensible for detection of RHD	less specificity, sometimes it can give false positive results	[28]
8	Biosensor and Nanosensor based diagnosis	Sensitivity and selectivity to the target analyte from a complex media	Disturbances produced on sensor surface due to ph changes and ionic strength	[31]
9	Catalase Test	Used to determine if bacteria produce the enzyme catalase.	If any RBCs are transferred than False positive results will result	[34]
10	Camp Test (Christie Atkins Munch-Petersen)	Identification of nonhemolytic group B streptococci and other ß-hemolytic streptococci.	Do not incubate in an anaerobic environment or under CO2.	[35]
11	Bacitracin susceptibility test	95% sensitivity for GAS, used to differentiate the beta- hemolytic Streptococcus.	Batch to batch variation present and can give false results for group G and C streptococci	[36]
13	Gram staining	Used to differentiate between gram positive and gram negative bacteria and also to examine cellular morphology	More characteristic observations appears in younger culture than in older. Gram negative results may occur in older culture.	[37]

Table 2. Comprehensive analysis of various methods used for diagnosis of RF

Preventive measures and treatment

a) Primary treatment

To avoid the initial development of RHD is the aim of primary prevention. It requires advancement in social factors of health like melioration in hygiene, housing and approach to health care [38]. Sufficient antibiotic therapy of GAS during sore throat so that it further helps decreasing the RF cases, is called primary treatment [39, 40]. Microbiological confirmation through throat culture or with a rapid antigen detection test (RADT) is requiring for proper and exact diagnosis of GAS pharyngitis [41]. If antibiotic are provided at the time of throat infections with symptoms of GAS infection then about 70% ARF risk will reduced [42]. GAS are susceptible to penicillin, carbapenems, cephalosporins [43].

b) Secondary treatment

The uninterrupted treatment with particular antibiotics to Patients with former attack of RF or RHD to prevent repeated approach of RF and it is called secondary treatment. Benzathine benzyl penicillin is commonly use antibiotic drug for prevention of RF attack [42]. For hypersensitive patients to penicillin, oral sulfadiazine or oral sulfasoxazole were used to decrease the progress of RHD medical therapies in former phase is advisable [44]. To prevent occurrence of ARF a precise diagnosis is require. There is a high risk for patients who have previous history for ARF for repeated attack of ARF. In prominent chance for repeated attacks of ARF continuous dose of intramuscular benzathine benzlpenicillin every four weeks and every three weeks is recommended. This leads to reduce RHD death rate [45]. Clinical examination on the basis of clinical history and physical findings is not more sensitive for RHD detection, so echocardiography should also used for detection [46]. If Electrocardiography and clinical examination then electrocardiography increased sensitivity to ten times for RHD diagnosis [47, 48].

c) Tertiary treatment

If heart valve are damaged after RHD then Tertiary treatment may prevent more damage by regular examination and surgery if require to that patients. If a patient with RHD have indication of mitral valve damage or if their left ventricular is not functioning properly then they are advised for surgery. Patients who regularly take secondary antibiotic prophylaxis for 10 years have beneficial prospectus with no noticeable disease [49, 50]. The patients who do not treated with antibiotics during secondary prophylaxis have high risk of recurrent attack of ARF during first 5 years [51].

Challenges

There are many challenges in prevention of RHD. To detect the asymptomatic GAS infections is not easy due to deficiency of approach to health care [41]. In developed countries, due to limited restrained resources it is challenging to diagnose and treat GAS pharyngitis. It is not easy to maintain a program to educate and aware the populations about the need of previous treatment for long period of time [52]. There is a big challenge to provide antibiotic, microbiological tests, surgery and other clinical facilities in developing countries [53]. Cost-effectiveness of screening test is also important [54].

Conclusion

It is clear that RHD is a major problem in developing and developed countries. The pathophysiology of disease need to be identified properly for a better understanding of disease and to reduce the False Positive Results. It is very important to develop sensitive and cost effective method for RHD detection for successful treatment and recovery of patients. Due to limitation of present available molecular and microbiology techniques, the new technology based on Biosensor for diagnosis should derived in use. With the advancement in the field of Biosensor the main challenge are to increase sensitivity, selectivity, reduce time for diagnose, cost effectiveness. In this review, the summary of all available methods for RHD diagnosis is provided.

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