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THE PROBLEM OF RF/RHD IN THE EASTERN MEDITERRANEAN REGION

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EPIDEMIOLOGY

(1) SOCIO-ECONOMIC FACTORS

It is now generally accepted that acute rheumatic fever (RF) is essentially a social disease. This concept is not new. In 1920, Poynton commented "the rarity of these cases of acute rheumatism in children in private practice as compared with hospital practice would form an interesting subject for inquiry" (1). In 1930 Glover wrote: "no disease has clearer cut social incidence than acute rheumatism. The incidence of acute rheumatism increases directly with poverty, malnutrition, overcrowding and bad housing" (2). The studies of Gordis et al (1969) in Baltimore (USA) showed that "race did not play a role in the epidemiology of RF, and that crowding or some factor related to it was one of the main environminents of rheumatic fever incidence" (3,4). Until only few decades ago, RF was described as a disease of the temperate climates, and was thought to be rare in the tropics and subtropics (5-7). The high incidence and prevalence of RF and rheumatic heart disease (RHD), subsequently reported from the tropics and subtropics (mostly developing) showed that this concept was erroneous (8-23). Instead, it has been realised that overcrowding and poverty are the two most important factors in the epidemiology of RF/RHD through out the world (24-26). However, in the world of RF/RHD, the old terminlogy of "temperate" and "tropical and subtropical", has been changed to "developed" and "developing". The new terminology is as misleading as the old. According to Disciascio and Taranta, "developing is a wishful thinking kind of word, as many developing countries are developing imperceptibly. We prefer the term "poor" which is what is usually meant" (26). Even in the most affluent countries, where pockets of poverty still exist, the eradication of RF/RHD remained an "unfulfilled hope" (27). Because of this strong impact of "poverty" on the epidemilogy of RF, the battle against the disease is not likely to be won by the Medical profession, even world wide, alone. Politicians, especially in the "developing" or "poor" countries should probably be involved.

(2) THE STREPTOCOCCAL PROBLEM

2.1 The Streptococcal Infections :

The epidemiology of RF, closely follows that of group A streptococcal (GAS) upper respiratory tract infections. The incidence of RF is greately influenced by the proportional incidence of GAS pharyngitis mainly in the childhood population and the magnitude of the host anitistreptococcal immune response. The proportional incidence of GAS pharyngitis and the magnitude of the antistreptococcal immune responses in the countries of the Eastern Mediterreanean Region are essentially similar to that of other countries (table 1 and 2). Inspite of this, the incidence of RF in the Eastern Mediterranean Region is higher than elsewhere (Table 3). This most probably reflects a high frequency of upper respiratory tract infections amongst the childhood population of such communities caused by a wide spread of infection, under the situations of poverty, particularly poor housing and overcrowding. This will be associated with a relatively higher incidence of GAS pharyngitis.

2.2 The Streptococcal Carrier Ship

The hemolytic streptococcal (all groups) carriership in tropical and subtropical (mostly poor) areas seems to be higher than that in temperate climate (mostly affluent) (39). Furthermore the prevalence of groups C and G is higher in the tropics and subtropics (39). Table 4. Shows that the pattern of prevalance in temperate climates is different from that in the tropics and subtropics. The prevalence of group A ranged between 54-61% in temperate climates against 14-30% in the temperate climates against 65 - 77% in the tropics and subtropics. What does this mean ? The answer is far from clear. However it seems that further work on the pathogenicity of groups C and G, together with close follow-up of these patients, is needed in countries where the prevalence of these two is high.

2.3 The Rheumatogenic Strains

The concept of a nephritogenic potential (nephritogenicity) of some streptococcal strains, based on significantly higher attack rates of acute glomerulonephritis (AGN) following GAS pharyngitis was pioneered by Rammelkamp and associates in 1952 (46, 47). This was soon supported by the findings that AGN following GAS pharyngitis was predominantly caused by a limited number of streptococcal strains mainly M12, M1 and M4. These types were called pharyngeal nephritogenic strans (48). Similarly, and soon after the term "impetigo strains" was coined by Parker and associates, based on the findings that a limited number of M non typable serotypes mainly belonging to the complex patterns T3/13/B3264, T/8/25/Imp. 19 and T5/27/44, accounted for the majority of cases of impetigo (49). This was supported by Dillon et al who, in addition, showed that these impetigo strains were different from those isolated from the throat of children with respiratory infections, in the same population (50). Subsequently many M typeable impetigo strains (e.g. M types 49,52,53,54,57 etc) were identified as nephritogenic (51-56). If there are nephritogenic and non-nephritogenic strains, another question must be raised : are there, similarly, rheumatogenic and non-rheumatogenic strains? The question is justified at least by observation that though both acute rheumatic fever (RF) and AGN follow group A beta haemolytic streptococcal (BHS) infection, rarely occur together simultaneously in the same patient at the same time (56, 57). However the concept of "rheumatogenicity" is less clear (57), though it gained a supporting epidemiological evidence from studies by Bisno et al and Majeed et al (58, 59). Do some group A streptococci vary in their "rheumatogenicity" as they do in "nephritogenicity"? In a recent review of the literature Bisno showed, that the number of streptococcal M types associated with well documented outbreaks of pharyngitis leading to AF was surprisingly small e.g. M types 5, 18, 19 and 24 (60). Furthermore, review of such outbreaks revealed that these serotypes (M types, 5,18,19 and 24) were frequently and consistently associated with RF, whereas other which are equally prevalent in the population (e.g. M12) have been rarely if ever implicated (60). Moreover in the pre-antibiotic era there are a number of epidemics of streptococcal pharyngitis in which infection not only failed to elicit first attacks of RF, but also failed to precipitate a recurrence in rheumatic patients (60). However the recent experience in Kuwait (59) showed that the majority of the group A streptococcal isolates from patients with RF, were M,T and SOF non-typable. The need for studying and identifying such non-typable strains is obvious.

THE INCIDENCE

The diagnosis of RF remains mainly clinical, as no specific diagnostic test, as yet, is available. Although the Revised Jone's Criteria (61) have certainly been helpful, over diagnosis and under diagnosis, are still unavoidable. Furthermore, the absence of efficient medical care delivery systems, serving the population at risk i.e. the "poor", makes it more difficult to obtain reliable data on the incidence and prevalence of RF and RHD in the Eastern Mediterranean Area. Taking this into consideration, the data on the incidence and prevalence of RF and RHD, from the Eastern Mediterranean Area (Table 3) should be viewed with caution. However, reliable data can be obtained in countries, where the medical care delivery system has been improving. Perhaps the recent experience in Kuwait, may serve as an example. Starting 1984, reliable data on the incidence of RF in Kuwait could be obtained. This was achieved by the establishment of a National Committee for the prevention of RF. Among the Committee members were the chairmen of all Paediatric departments of the regional hospitals

in Kuwait, the physicians in charge of the primary care centres and the child welfare centres (0-12years) an epidemiologist and a stastician. The policy of the Committee, stressed that the prevention of RF should be an integral part of the primary care delivery system. This insured that all children suspected of developing RF in the primary care and child welfare centres, were referred to the paediatric departments of the regional hospitals, where the diagnosis was assessed. The revised Jone's Criteria (61) were accepted as the diagnostic criteria to be used by all. Statistics, prepared by the chairmen of the paediatric departments were collected and assessed once every three months. This insured, reasonably reliable data, and at the same time decreased the chances of missing cases in the primary care centres. Through this, it was possible to estimate the annual incidence of RF in the country as 39/100.000 and 31/100.000 childhood population (5 - 14 years) in the years 1984 and 1985 respectively (62).

THE CLINICAL PICTURE

Recently studies from "developed" countries have reported a decreasing incidence and severity of RF (63-67). In contrast, reports from the Eastern Mediterranean Region described a different clinical profile in which the incidence and severity of carditis, congestive heart failure and motality were high. However the studies from the Eastern Mediterranean Region were retrospective, reported from tertiary referral centres, and have failed to differentiate between initial attacks, recurrences, and already established cases of RHD (8-16). Recent prospective studies of the INITIAL attack of RF, from the same region (18,19), reported a mild form of the disease, similar to that described in developed countries (Table 5), and attributed this to the prospective design of their studies and the inclusion of initial attack only in a general pediatric population (18,19). The low mortality rate (0.5% and 0.9%) reported in the two recent prospective studies (18,19), contrasted sharply with the high mortality rate reported from neighbouring countries (Table 5). Similarly, studies from the Eastern Mediterranean Region reported a high prevalence of RHD with the development of EARLY cardiac surgery in children and adolescents (12-14). These findings were different from those from developed countries, giving rise to the possibility that the evolution of RHD behaved differently in this Region with a tendency for earlier development of a severe valvular RHD (12-14). These studies, however, were retrospective in nature, reported from tirtiary referral centres and no effort was made to differentiate between initial attack and recurrences. These findings have been challenged by two recent studies (70,71). Data from these studies (70,71) showed that the evolution of RHD in the Eastern Mediteranean Region (tropics and subtropics) was not different from that described earlier in the developed countries or countries with temperate climate (Table 6). Analysis of the recent studies (70,71) from the Region and comparison to those reported from other countries, clearly showed that when the initial attack of RF was studied in the general childhood population (to avoid bias seen in tertiary referral centres) while carefull excluding recurrences and already established case of RHD, and with patients followed up the same group of physicians (to avoid subjective auscultatory differences) in a prospective way, and insuring compliance with secondary prophylaxis, the evolution of RHD following the initial attack of RF behaved similarly in the different climates and countries (Table 6). The higher prevalence of RHD and the early development of severe valvular involvement, seen in the "developing" countries, probably reflect the well documented role of recurrence in inflicting further cardiac valvular damage (75-77) and illustrates the failure of the medical care delivary system in protecting the rheumatic children from recurrences.

PREVENTION

There are four known strategies for prevention of RF/RHD :

1. Primary Prophylaxis
2. Secondary Prophylaxis
3. Vaccination
4. Improvement of the socioeconomic status of the population at risk.

PRIMARY PROPHYLAXIS

Pharyngitis is a common disease in the community, especially in childhood. The annual incidence of pharyngitis in all school-aged children is estimated to be around 11%(78). Twenty percent of pharyngitis in such children is caused by GAS and 80% by non-bacterial, presumably viral agents (28-31). The role of GAS in the aetio-pathogenesis of RF is beyond dispute (79). The concept of primary prophylaxis is based on the findings of the well documented studies of Denny (80) and Wannamaker (81). Data from these studies have shown that when antibiotics were given early in the course of GAS pharyngitis, a significant drop in the attack rate of RF was achieved (80, 81). Thus primary prophylaxis is an ideal form of prevention. However, several problems have rendered it a difficult goal to achieve. The main problem comes from the unreliability of differentiating GAS pharyngitis from viral pharyngitis on clinical ground alone (29, 82-84). A rencent study of current primary prophylaxis, based on clinical judgement alone, in a primary care clinic in Kuwait, has revealed disturbing data (29). Data from this study showed a very high false positive diagnosis of GAS pharyngitis (76%). This implied that the great majority of patients with pharyngitis would have been given unnecessary antibiotics. On the other hand, a similar high false negative (46%) diagnosis of GAS pharyngitis, implied that almost half of the patients with GAS pharyngitis would have been denied antibiotic treatment with the possibility that some would develop the sequelae. The introduction of bacteriological diagnostic facilities in primary care clinics is a tempting solution to the problem. However this also has two difficulties. The first is that it is costly and may not prove to be cost-effective. The second is that, standard bateriological diagnostic facilities, for the diagnosis of GAS pharyngitis, necessate a period of 48 hours, before the results are available. This necessates a second visit to the clinic. In the experience of many, including ourselves, parents were reluctant to make a second visit. This leaves the current primary prophylaxis regimen with many difficulties. There is a room for hope however, a newly introduced direct swab test for the detection of GAS directly from the throat has proved to be highly sensitive and specific and could be carried out in two minutes (85). This is expected to solve the important diagnostic problem. Furthermore a recent study from Kuwait has shown that a single intramuscular injection of benzathine penicillin in the treatment of GAS pharyngitis was successful in 97% of cases (29). This is expected to solve the therapeutic problem of non-compliance to a 10 days course of oral penicillin. Based on the results of these two studies (29, 85), a new regimen based on the rapid diagnosis of GAS pharyngitis, by the two minute direct swab test and the prompt effective treatment of GAS pharyngitis by a single intra-muscular injection of benzathine penicillin may make primary prophylaxis a practical possibility. However, in the light of the experience of other investigators, where only a minority of patients with pharyngitis seeked medical advice a complete success of "Primary Prophylaxis" with total eradication of RF in the community should not be expected (86).

SECONDARY PROPHLAXIS

This aims at prevention of recurrences. The recurrences of RF are now, well known to be precipitated by new straptococcal infections (79). However not all strains of GAS are capapable of precipitating a recurrence (60). In the natural history of RF and before the antibiotics era, the recurrence rate varied between 66-85%(87-89). The contineous administration of antibiotics was shown to be effective in reducing the frequency of recurrences (90-93). In a recent study in which 126 children with the initial attack of ARF, were followed up prospectively for a mean period of 6 years the recurrence rate was 0.005/ patient/year follow up in those patients, who maintained regular secondary prophylaxis i.e. 0.5% patient/year. Compared to 0.2/patient/year in those patients who did not maintain regular secondary prophylaxis i.e. 20% patient/year (71). Recurrences were shown not only to inflict further damage to valves already affected, but also to affect valves that escaped damage initially (71). In previous and recent studies the reduction of the prevalence rate of RHD, by secondary prophylaxis, was obvious and significant (71-74). However, to achieve such results, the questions of which antibiotic to use, the route of administration, the frequency and dose of parenteral benzathine penicillin G and the duration of secondary prophylaxis should be answered.

1. Which antibiotic ?

Sulphadiazine, in a dose of 0.5-1 gm daily, has been shown to be effective in reducing the recurrence rate to 2.8%/patient/year (94). Salphadiazine is an inexpensive drug, but it carries with it the risk of non-compliance (oral route), emergence of resistant strains of GAS(95) and side effects. Penicillin is a superior antibiotic. It is not expensive, toxicity and hypersensitivity reactions are rare, it is effective and resistance has not been reported so far.

2. Route of administration

The oral use of penicillin V was shown to reduce the recurrence rate to 5.5%/patient/year (94). The risk of oral penicillin is non-compliance. Parenteral benzathine penicillin G has been the most commonly used in secondary prophylaxis and has been shown to be the most effective. Table 6 shows that it is still effective in the eighties as it was in the sixties.

3. How frequent should parenteral benathine penicillin G be given ?

The once/monthly injection has been shown to be effective (Table 6). Furthermore it is easy to remember by the child and the family. However giving the injection once/3 week, has been claimed to be more effective (96). This is not easy to remember and could affect compliance. The dose of benzathine penicillin G is 1.2 million units for children aged six years or above and 600.000 units for children younger than six years.

4. How long should praphylaxis be maintained ?

To answer this question, one should consider the different variables affecting recurrences, namely the interval since the initial or antecedent attack, the presence or absence of carditis and the age of the patient. The majority of recurrences occur within the first 3-5 years after the antecendent attack. In a recent prospective study of recurrences and a mean followup period of six years, 90% occurred within the first three years, 9% in the fourth year and 1% in the fifth years (71). The concept that patients with corditis are more likely to develop recurrences than patients with no cardiac involvement has been well documented in several studies (71,97,98). However a very important question remains : does carditis develope during a recurrence, in a patient who did not manifest carditis in the initial attack? There is good evidence that if the host escapes carditis in the initial attack, he or she will continue to do so in subsequent recurrences (71, 76, 77). The age of the patient is also important. The younger the child at the time of the initial attack, the greater the likelihood of recurrence (99) and the incidence of recurrences tends to decline with age after puberty (99). Taking these factors into consideration, the regimen of secondary prophylaxis, should probably be selective: those patients with cardiac involvement in the initial attack, should continue prophylaxis at least till the age of 25 years, possibly for five years (71, 75). Because of the documented occurence of carditis, during a recurrence, in a patient who had 'pure' chorea initially, one attack of chorea is an indication for long term prophylaxis (? till the age of 25 years) possibly for life (71,75-77). Despite the effective rate of secondary prophylaxis in reducing the incidence of occurances and the prevalence of RHD in the community, they are still high in the Eastern Mediterranean Region (8-23). This indicates that secondery prophylaxis is not carried out faithfully on a large scale in such countries. The main cause of this is the non-availability of efficient health care systems that can reach and deliver the medical care to people at risk i.e. the poor. The cost can be projected as a problem, but it should always be stressed that prevention is much cheaper than open heart surgery and is more cost effective. It was not surprising, therefore, that the discission taken by the RF Prevention Committee of the ISFC, during its first meeting in 1983, was to adopt secondary prophylaxis as the best and most practical means of prevention at present.

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Table 1

The proportional incidence of group A streptococcal (GAS) pharyngitis in the Eastern Mediterranean Region; comparison with other countries.

Country	Year	Ref. (No.)	No. of patients	GAS* Pharyngitis (%)
Egypt	(1973)	(28)	156	19%*
Kuwait	(1984)	(29)	465	22%*
India	(1971)	(30)	248	14%*
USA	(1974)	(31)	5500	23%*

* Numbers are expressed as percentage of the total number with Pharyngitis.

Table 2

The antistreptococcal immune responses in children with rheumatic fever in countries with different climates.

Author	Ref. (No.)	Country	Climate	No. of Patients	GMT ASO	GMT AH
Bernhard & stollerman	(32)	USA	Temperate	31	497	578
Limson et al.	(33)	Philippines	Tropical	NA	419	NI
Majeed et al.	(34)	Kuwait	Subtropical	130	488	595

GMT : Geomatric mean titer. ASO : Antistreptolysin O.

AH : Anti hyaluro dinase. NI : No information.

Table 3

The incidence of RF in countries of the Eastern Mediterranean Region. Comparison with other countries.

COUNTRY	YEAR	(REF) (NO.)	INCIDENCE (PER / 100,000)	AGE GROUP (YEARS)
KUWAIT	1985	(35)	31	5-14
IRAN	1972	(36)	58-100	ALL AGES
CYPRUS	1972	(36)	27-43	ALL AGES
SWEDEN	1985	(37)	0.2	0-15
USA	1978	(38)	9*	5-14
ENGLAND	1963	(36)	4.7	1-14

* 2.7 in all ages.

Table 4

Prevalence of the different serogroups of B-hemolytic streptococci(BHS) in normal asymptomatic school children in Kuwait: comparison with similar studies from temperate, subtropical, and tropical countries

Country	Reference No.	Climate	Years of study	No. of children	BHS Carrier rate (%)	Groups* A	C+G (%)	Others (%)
Czechoslovakia	(40)	Temperate	1967-1971	244	11.6-19.3	54	22	24
Netherlands	(41)	Temperate	1964-1965	412	51	61	28	11
Egypt	(42)	Subtropical	1967-1970	156	50	30	70	
Kuwait	(39)	Subtropical	1978-1979	1041	47	22	74	4
Liberia	(43)	Tropical	1965-1966	72	49	20	65	15
Nigeria	(44)	Tropical	1971-1972	424	8	21	77	2
South India	(45)	Tropical	1957-1958	883	49	14	67	19

* Numbers expressed as percentage of the total.

Table 5

The clinical profile of acute rheumatic fever in studies reporting the inital attack only.

Clinical profile	Massel et al. 1958 (457 patients) (Boston, U.S.A.) (Ref. 68)	Feinstein and Spagnuolo 1962 (275 patients) (New York, U.S.A.) (Ref. 69)	Sanyal et al. 1974 (102 patients) (New Delhi, India) (Ref. 18)	Majeed et al. 1981 (210 patients) (Kuwait) (Ref. 19)
Arthritis	74%	76%	66.6%	79%
Carditis	52.5%	41.8%	33.7%	46.2%
Cardiomegaly without CHF	NI	10.9%	9.8%	10%
CHF	7.9%	5.8%	2%	4.8%
Pericarditis	6.3%	3.3%	1%	1.4%
Chorea	23%	7.6%	20.5%	7.6%
Erythema marginatum	10.5%	1%	1.9%	1.4%
Subcut. nod.	11.8%	4%	1.9%	0.5%
Mortality	1.6%	0.36%	0.98%	0.48%

NI, no information; CHF, congestive heart failure; Subcut. nod., subcutaneous nodules.

Table 6

THE EVOLUTION OF RHEUMATIC HEART DISEASE IN PATIENTS ON REGULAR SECONDARY PROPHYLAXIS IN THE DIFFERENT CLIMATES

Study	Ref.	Year Ref.	Climate	Patients N	Patients No./years	Recurrences N	Recurrences RR**/patient/yr	RHD* N	RHD* PR***
U.K. - U.S. joint report.	(72)	(1960)	Temperate	324	1620	42	0.026	101	31%
Feinstein et al.	(73)	(1964)	Temperate	156	260	2	0.004	NA†	NA†
Tompkins et al.	(74)	(1972)	Temperate	115	565	1	0.001	30	26%
Sanyal et al.	(70)	(1982)	Tropical	65	325	2	0.006	23	35%
Majeed et al.	(71)	(1986)	Subtropical	66	383	2	0.005	15	23%‡

* RHD : Rheumatic heart disease. **RR : Recurrence rate

***PR : Prevalence rate. † Not available.

‡Not significantly different from the other studies ($p > 0.05$).