The Turkish Journal of Pediatrics 32:249 - 258, 1990

LONG – TERM PROGNOSIS OF ACUTE RHEUMATIC CARDITIS WITH COMBINED AORTIC AND MITRAL REGURGITATION*

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Summary: Onat, T, Ahunbay G. (Pediatric Cardiology Unit, Department of Pediatrics, Istanbul University Cerrahpaşa Faculty of Medicine, Istanbul, Turkey). Long-term prognosis of acute rheumatic carditis with combined aortic and mitral regurgitation. Turk J Pediatr 32: 249-258, 1990.

Thirty-one patients with acute rheumatic carditis associated with aortic (AR) and mitral regurgitation (MR) who received corticosteroid anti-inflammatory therapy for an average of nine weeks were followed up for 332 patient-years (mean: 10.71 years). The age of onset was 9.34 (1 SD = ± 1.94) years. The patients were classified according to degree of left ventricular volume overloading (LVH), duration of pre-treatment interval and regularity of penicillin prophylaxis. The probability of the yearly disappearance of MR, AR and both lesions were calculated for the total group and in relation to affecting subgroups. The mean yearly rate of disappearance of AR was 2 percent after a 10 percent probability in the first year. This rate was 6.83 percent per year for MR, and it increased to 10.15 percent per year in the patients in whom therapy was initiated in less than three weeks, and decreased to 3.14 percent in the patients in whom therapy was initiated after three weeks. The disappearence of both AR and MR was observed in only two patients (about 1% per year); MS developed in two patients (6.45%) and the mortality rate was 3.2 percent in 332 patient-years (0.0001/year). *Key words: acute rheumatic fever, penicillin prophylaxis, prognosis.*

In acute rheumatic fever, aortic regurgitation (AR) is usually combined with mitral regurgitation (MR). The occurrence of MR in patients with AR is reported to vary between 50[1] and 93 percent[2], most reports ranging between 71 and 92 percent. These incidences vary greatly in studies because a portion of the data has been obtained from the records of patients who have experienced initial attacks, have had recurrences, or who have been over-diagnosed for AR in some centers[3-5].

Long and short-term studies reporting the incidence of residual heart disease (ResHD) have neglected to differentiate the outcome of each lesion when they co-exist[1-8]. Information regarding the prognosis of each lesion has been obtained from patients with either isolated MR or AR, or from a combination, which

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includes mitral stenosis (MS) with MR. In general, isolated MR has a better prognosis than isolated AR. It is not known, however, whether this also applies if the lesions occur together because studies have been planned to determine ResHD. Thus, MR, having a better prognosis and a greater probability of disappearing, is obscured by such an analysis, i.e., in case of persistent AR.

The prognosis of valvular lesions depends on such factors as severity of the lesion, presence of congestive heart failure (CHF), prevention of recurrences, and time of onset of effective treatment[9]. We therefore present our follow-up results of 332 patient-years of each lesion in 31 patients in whom AR and MR coexisted, whereby factors influencing the prognosis such as degree of left ventricular volume overloading, presence of CHF, regularity of penicillin prophylaxis (PP) and the duration of the pre-treatment interval were considered.

Material and Methods

The study population comprised 31 children who had an initial attack of MR and AR due to rheumatic fever[10], and who had been hospitalized in the Department of Pediatric Cardiology, Cerrahpaşa Faculty of Medicine, between 1964-1984. Their laboratory studies were complete with regard to the methodologies presented below. They were followed up for 2-21 years by the same pediatric cardiologist (T.O.), who was informed of the past histories of the patients and who had prospectively carried out the follow-ups at the Out-patient Department of the unit.

The course and prognosis of the condition were evaluated with respect to 1) pre-treatment interval; 2) adherence to penicillin prophylaxis (PP);3) presence of congestive heart failure (CHF), and 4) presence of valvular lesion and degree of left ventricular hypertrophy (LVH).

1) *Pre-treatment interval.* The pre-treatment interval was considered as the time which had elapsed between the onset of symptoms attributed to acute rheumatic fever (ARF) and the initiation of antiinflammatory therapy. If proper therapy was instituted more than three weeks after the onset of the initial symptoms, these patients were classified as the "late group", in contrast to the "early group".

2) *Adherence to penicillin prophylaxis.* Following the initial ten days of penicillin therapy, penicillin prophylaxis, consisting of benzathine penicillin in a dose of 1,200,000 units, was initiated on the eleventh day. The patients who showed strict adherence to the regimen every 3-4 weeks were classified as the "regular PP" group, while those who had neglected to take the drug for a few months or for a longer period, but who had later resumed taking it on a regular basis, were classified as the "irregular" group. All the patients received prednisone in a dose of 2 mg/kg/day for a duration of three weeks, which was followed by a gradual reduction of dosage for another six weeks.

3) *Presence of congestive heart failure.* Patients with carditis were considered to have CHF, if dyspnea not caused by a respiratory infection was present, and if cardiac enlargement was not due to pericarditis. Thus, false positive diagnoses of CHF, which are most common, were avoided.

4) *Presence and degree of valvular lesion.* A newly observed pansystolic murmur maximum at the apex of grade II-IV intensity, transmitted towards the axilla during the hospitalization period, was accepted as MR. An early diastolic decrescendo murmur maximum at the 2nd and 3rd left parasternal intercostal space was accepted as AR. The valvular lesion was considered healed if the specific murmur had disappeared and was also undetectable after exercise, including subsequent check-ups.

The degree of severity of both valvular lesions can be assessed from the degree of left ventricular volume overloading[11,12], which can in turn be evaluated from electrocardiographic voltage dependent LVH criteria[12] and also from the cardiothoracic ratio (CTR) using p.a. teleradiography. Both methods used simultaneously reduce the false negativity or false positivity of either system. The CTR can be false positive in pericardial effusion and in the expiratory phase[13]. A right diaphragmatic level of one intercostal space higher in the same individual leads to a mean increase of 7 percent in CTR[13]. In comparing the values in the same subject and in classifying CTR values, a correction was made according to Onat[13], which was designated to standardize all CTR values to a right diaphragmatic arc's level of under the 5th anterior rib.

In order to correct the false positive cardiac enlargement, due to pericarditis, which was observed on the chest x-ray, the values that were used as an index were those obtained after the serial clinical detection of pericarditis, and not those which had been obtained at the initial examination.

Taking into account the above-mentioned points, left ventricular volume overloading (LVH) was graded into three groups of severity[9].

Follow – up of patients: The prognosis of acute rheumatic carditis associated with MR and AR was based on the monitored 332 patient-years of the 31 subjects studied. Of the initial 31 patients, 21 were followed up for ten years or more. The mean follow-up period was 10.7 years and the median value 11 years. Ninety-four percent were followed up for four years, 81 percent for six years, 77 percent for seven years, 68 percent for ten years, 23 percent for 13 years, and 13 percent for 20 years. Of the ten patients who were unable to be followed up for ten years, two were followed up for two years, four for four years, and four for seven years.

The distribution of the data of patients "lost to study" in a longitudinal study can lead to biased results if it is significantly different from that of the subjects remaining in the study. Therefore, a chi-square test was performed to determine the differences in the qualifications of the subjects who were lost to study in

different years in relation to the degree of severity of LVH, percentage of patients with CHF (10% vs. 19%), pre-treatment interval (60% vs. 50%) and percentage of patients with regular PP (50% vs. 52%). The distribution of the data of the cases lost to study did not differ significantly from the distribution of the data of the initial material. Thus, the yearly rate of disappearance of MR or AR in our subjects was considered unbiased data.

Linear regressions estimating the yearly rate of disappearance of MR, AR and of both lesions were calculated from the yearly percentage of patients without the specific lesion/total patients studied for that year.

Results

The number of patients in the above-specified subgroups of the classification system and their age and sex distribution are presented in Table I.

The age of onset of carditis was 9.34 years, with a range from 4.7 to 13.1 years. The well known male preponderance in patients with AR is 67.7 percent, which was significant when compared with the 42 percent male incidence observed in our 86 isolated MR patients[9] ($x^2=5.134$; $p<0.025$). Although early onset of treatment was more often (65%) associated with regularity in the continuation of PP, as compared with late onset of treatment (36%), this difference was not significant ($x=1.553$; $p>0.20$).

The mean severity of LVH, graded from I-III was 1.82 in patients with a short pre-treatment interval as compared to 2.07 in patients with a longer than three week interval. Likewise, 42 percent of patients with LVH (groups II-III) were in the early treated group. The difference was not statistically significant ($x^2=0.120$;

Table I: Number of Patients in the Classification System and their Age and Sex Distribution

Left Ventricular Overloading	Penicillin Prophylaxis	Onset of Therapy Early*	Late**	CHF***	Sex male	Sex female	Age mean SD
none or moderate	regular	10	3	1	9	4	9.19 1.80
	irregular	5	6	1	8	3	
severe	regular	1	2	1	3	–	9.88 2.37
	irregular	1	3	3	1	3	
Total	regular	11	5	2	12	4	9.34 1.94
	irregular	6	9	4	9	6	
		17	14	6	21	10	

* "Early" denotes a pre-treatment interval of less than three weeks.
** "Late" denotes a pre-treatment interval of more than three weeks.
*** CHF: Congestive heart failure.

$p>0.70$). The incidence of regularity with regard to continuation of PP was not significantly different in those with or without LVH ($x^2=0.013$, $p>0.80$).

Disappearance of AR: The pulse and diastolic pressure were normal in three patients. The diastolic pressure was below 55 mmHg in 13 patients and below 35 mmHg in 15 patients. Thus, celer pulse and low diastolic pressure were present in 28 of the 31 patients. Of the 25 patients followed up for six years, AR disappeared in four patients in the first year, in one patient in four years, and in one patient in five years, which constitutes a 25 percent rate of disappearance of AR. After six years, there was no disappearance of AR in any of the patients. Of the six patients who recovered from AR, none had severe volume overloading. Five patients were receiving continuous PP and had no recurrence, while one patient, who was receiving irregular PP, did. The yearly rate of disappearance of AR can be estimated from the regression presented in Table II, Fig. 1. This rate is about two percent per year, after a 10 percent probability in the first year. However, if there is no LVH present at onset, the probability of AR disappearing is about 15 percent in the first year, and 3.5 percent per year in the following years.

In 24 patients in groups I and II, i.e., with either no or moderate LVH, the recovery rate of AR was found to be 29 percent in five years and 30 percent in ten years.

The yearly rate of disappearance of AR was 2.01 percent, 3.4 times less than MR (Table II, Fig. 1).

Table II: Linear Regressions of Yearly Disappearance Rates of Rheumatic Valvular Lesions

		Regression analysis for disappearance of valvular lesions in MR and AR	
	No. of Patients	Disappearance of MR (%)	Disappearance of AR (%)
Total	31	6.83 (years) − 3.82	2.01 (years) + 8.82
Late**	14	3.14 (years) + 1.90	1.82 (years) + 3.12
Early*	17	10.15 (years) − 8.95	2.18 (years) + 13.60
LVH:			
None or moderate	24	7.19 (years) − 1.73	2.31 (years) + 11.90
severe	7	3.41 (years) − 5.68	0.00 (years) + 0.0
		Disappearance of both MR and AR (%)	
	31	0.93 (years) + 0.55	

* "Early" denotes a pre-treatment interval of less than three weeks.
** "Late" denotes a pre-treatment interval of more than three weeks.

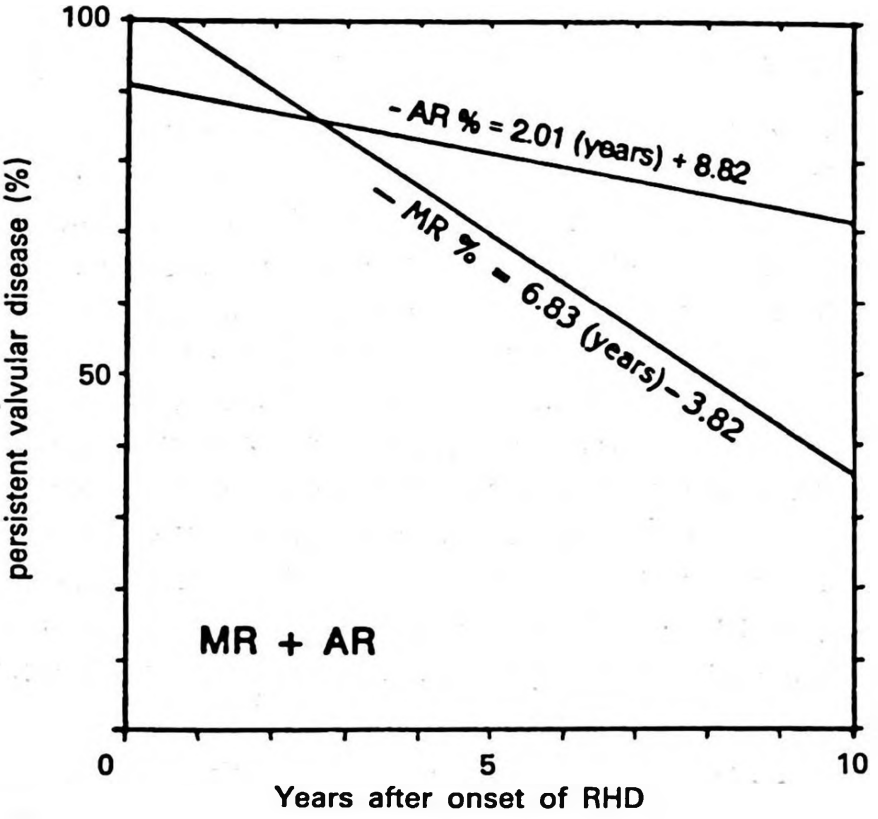

Fig. 1: The percentage of patients with persistent aortic regurgitation (AR) and mitral regurgitation (MR) in relation to years after onset. The regression equations are presented in percentage of disappearance of AR (−AR%) and MR (−MR%), whose slopes represent the yearly probability of disappearance of regurgitation. Note that the chances of recovery are higher in MR than in AR. The slopes represent a yearly percentage of disappearance of 6.83 as compared to 2.01, respectively. But note that the recovery rate in the first years is higher in AR than in MR.

Disappearance of MR: The yearly probability rate of disappearance of MR was 6.83 percent. The expected median time of disappearance was 7.9 years. This tendency of recovery decreased to 3.41 percent per year in the group with severe LVH, while it increased to 7.78 percent in those with or without moderate LVH (Table II).

The yearly rate of disappearance of MR was 10.5 percent in patients in whom therapy was initiated in less than three weeks, and 3.14 percent in patients in whom therapy was initiated after three weeks (Table II; Fig. 2). The higher rate of disappearance of MR observed, in the earlier treated group, was not significant in five years ($x^2=0.588;p>0.40$) but significant in ten years after the onset of rheumatic heart disease ($x^2=5.86;p<0.025$).

Disappearance of both AR and MR: Both AR and MR disappeared in only two patients: one in the second and another in the fifth year, which constitutes nearly a 0.93 percent chance of complete recovery per year (Table II). Congestive heart failure was present in six patients (19%) at onset. Treatment started after three weeks in five patients, and in less than three weeks in one. There were no

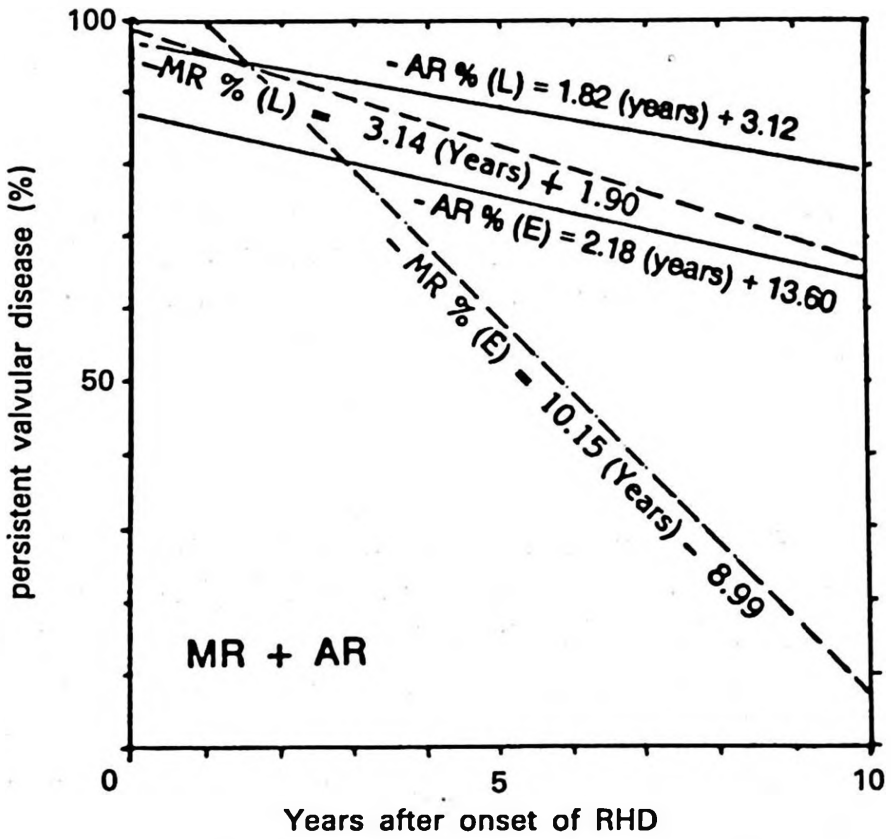

Fig. 2: Same coordinates as in Figure 1. The rate of disappearance of MR (broken lines) and AR (continuous lines) are divided into two groups in relation to onset of therapy before or after three weeks. Note that the chances of recovery are higher in the earlier (E) treated groups as compared to the later (L) treated groups.

patients with CHF at onset without ResHD after ten years, and no patients who had recovered from AR. The development of MS was observed in a female patient with CHF and in a male patient (6.45%). In the latter, AR disappeared in the second year and MS developed in the fourth year after the onset of MR.

Course of patients with ResHD after ten years: In one patient without LHV, AR and MR persisted without LVH developing in 20 years. In the group with moderate LVH, MR disappeared in one patient after 12 years and persisted in another patient for 14 years, without LVH developing. AR was still present after 21 years in two patients, and in three other patients after 16, 14 and 13 years, respectively. In one male patient from the group with severe LVH, after two recurrences in the sixth and seventh year (despite regular PP), MR disappeared 16 years after its onset, however, AR, was still present after 21 years.

Recurrences (R): Of the 12 cases with recurrences, there was only one patient who recovered from AR (8.5%) and six from MR (50%). Of the 19 patients without recurrences, five recovered from AR (26%) and 11 from MR (58%). In the regular PP group, the recurrence rate was 2.42% per year in 165 patient-years (four in three patients' 41 years and no R in 13 patients' 124 years) and 8.67 percent per year in the 150 patient-years of the irregular PP group. The differences

in recurrences between the groups receiving regular and irregular PP was significant ($x^2 = 3.950$; $p<0.05$), but differences were much more significant in our 730 patient-years of isolated MR cases[9].

Mortality: One patient, who discontinued PP, died in the fourth year during a recurrence of pancarditis. The mortality rate was therefore calculated as 3.2 percent of the total AR and MR patients in 332 patient-years (0.001/year) and 17 percent of the patients with CHF who were followed up for 54 patient-years (0.003/years).

Discussion

The prognosis of MR and AR differed in the same patient, in that the recovery rate in MR was lower in the first two years and much higher in the years thereafter (Table II, Figs. 1, 2). It is evident from Fig. 1 that the slope representing the disappearance of MR is 3.4 x higher but the intercept is negative, 3.8 as compared to a positive 8.8 in AR.

The chance of recovery from AR is around 20-25 percent. This becomes, however, less probable after two years of onset and much less after five years.

The results reported in the "Joint Study"[4,5] with regard to the first year are consistent with our findings. The investigators, however, reported data from one center where AR had been over-diagnosed, and the rates of disappearance of AR were extremely high as compared to all the other centers (24/33=73%). Therefore, they excluded the results of this center[5]. However, only 12 patients remained from 11 centers, and only three of these recovered (25%), which is consistent with our findings obtained after ten years. Bland and Jones[6] have observed that if the intensity of the AR murmur is grade I, the probability of it disappearing is 33 percent (9/27) while, if the intensity of the AR murmur is grade II or higher, the probability of it disappearing is nil.

Wilson and Linn[14] found that in 96 adult patients with isolated AR,the murmur did not disappear. However, the intensity of the murmur regressed in 15 percent of the patients and remained constant in 85 percent.

From the eight isolated and 17 combined AR patients that Thomas[15] studied, all revealed significant AR, and the condition did not disappear in five years, while in the cases with slight AR, 8/10 disappeared.

In our subjects, the rate of disappearance of AR plus mitral valve disease was 13.1 percent (9/69), as compared to 45.7 percent in isolated AR (19/35) in the series of Feinstein et al[7]. This was reported as two percent (1/49) in another publication describing the same patient series[8]. The rates of disappearance were given for both lesions but not for each. No differentiation was made between MR and MS

with respect to prognosis of combined valvular lesions. In their patients with isolated AR, the rate of disappearance was 27.8 percent (5/18).

We conclude, that in patients with rheumatic carditis and combined mitral and aortic regurgitation the chance of recovering from AR is about 10 percent in the first year and 19 percent in five years. On the other hand, the chance of recovering from MR is much better; 30 percent and 65 percent in five and ten years, respectively. But the chance of complete recovery from both valvular lesions is only 6.5 percent in ten years or more. This is the reason why isolated AR is found much more frequently in adult patients.

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