

STUDY OF RISK FACTORS AND LABORATORY PROFILE IN UNDER 15 YEARS AGE GROUP CHILDREN WITH ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

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ABSTRACT: CONTEXT: BACKGROUND: Acute Rheumatic fever / Rheumatic Heart disease is the most common acquired childhood heart disease diagnosis made in India and is consistently associated with poverty and overcrowding. There is no single symptom, sign or laboratory test that is diagnostic of Acute Rheumatic fever and carditis. Revised, edited and updated Jones criteria are guidelines to assist practitioners and are not a substitute for clinical judgment. The main concern in liberalizing these criteria in developed countries may be over diagnosis of Acute Rheumatic fever. **AIMS & OBJECTIVES:** To study the risk factors and laboratory profile in children with Acute Rheumatic fever / Rheumatic Heart disease. **MATERIALS & METHODS:** The Study was conducted for 2 years period in a tertiary care hospital on less than 15 years children diagnosed as Acute Rheumatic fever / Rheumatic Heart disease. **RESULTS:** In our study all the cases (100%, 36 cases) belongs to Lower socio economic status. Overcrowding is noted in all 36 cases (100%) and we noticed rural predilection in 91.7% (33 cases) cases. **CONCLUSION:** Basing on the results of our study we conclude that lower socio economic status, overcrowding (100% cases) and rural predilection (91.7%) are frequent associate risk factors of Acute Rheumatic fever / Rheumatic Heart disease. Further we found Anemia (88.89%), positive C.R.P (86.11%), and A.S.O titer more than 400 I.U/ml in (69.44%) as common laboratory abnormalities.

KEYWORDS: Acute Rheumatic fever, Rheumatic Heart disease, Polyarthrititis, Arthralgia, CRP, ASO titre, Cardiomegaly.

INTRODUCTION^{1,2}: Rheumatic fever is a multi-systemic disease affecting primarily the heart, joints, brain, cutaneous and subcutaneous tissue secondary to an immune reaction to Group A Beta hemolytic streptococcal infection by rheumatogenic strains 1, 3, 5, 6, 18 and 24. Acute Rheumatic fever / Rheumatic heart disease is the most common acquired childhood heart disease diagnosis made in India. Rheumatic fever is characterized by a number of clinical and laboratory abnormalities, the combination of which makes the diagnosis very probable.

A number of studies have suggested that, of the various manifestations of poverty, crowding, which contributes to the spread of group A streptococcal infections, is the one most closely associated with the incidence of Acute Rheumatic fever. The available data regarding prevalence rate for Rheumatic heart disease in India was 2/1000 in the village population and 2.07/1000 for women and 1.23/1000 for men in the urban population. The group A Beta hemolytic streptococcus causes Rheumatic fever is a firmly established fact and though there is no experimental model to support this fact, clinical, epidemiological immunological evidence is there to support this fact. Rheumatic heart disease constitutes from 16.5 to 50 percent of the cardiac patients in a hospital. A survey of 11 cities in India showed a prevalence rate of 0.55 to 0.67/1000. A survey conducted by the Indian

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council of Medical Research (ICMR) involving 133, 000 children 6 to 16 years in age showed the incidence to be 5.3/1000. Whereas incidence of Rheumatic fever following streptococcal throat infection in the western countries is 0.3 percent in the general population and 1 to 3 percent in crowded communities like army barracks. The attack rate has come down to as low as 0.2/ lakh population in developed countries while it remained high in developing countries. This shows the magnitude of the problem in the country.

EPIDEMIOLOGY³: A number of factors affect the incidence of Rheumatic fever from their effect on frequency of Streptococcal attack. These include age, economic level, crowding, climate, altitude and temperature, and available medical care. Most common age group is 5 -15 years and less common in children less than 5 years of age. The most consistent predisposing factor appears to be crowded living conditions with close person-to-person contact and inadequate treatment and prevention of Streptococcal infection as shown by high incidence of Rheumatic fever in Mooris in Newzealand who live in more crowded conditions than that of remaining population.

Host factors are also known to play an important role in incidence and also clinical manifestation of Rheumatic fever, Monozygotic twins have higher concordance rate for Rheumatic fever than dizygotic twins suggesting a genetic factor.⁴

DIAGNOSIS OF RHEUMATIC FEVER: Paucity of criteria to diagnose Acute Rheumatic fever led to dilemma which resulted in under diagnosis or over diagnosis and this prompted Ducket Jones from Boston to propose a set of criteria to diagnose Acute Rheumatic fever. He sub grouped these criteria into major and minor, neither of them having any prognostic connotation in the year 1944.⁵ These original criteria did not differentiate between Arthritis and Arthralgia and Erythema marginatum was classified as minor criteria. Subsequently, the original Jones criteria have been modified four times. The latest revision by American Heart association was made in 1992.⁶

Diagnosis of Rheumatic fever is based upon satisfying the Jones criteria [updated 1992]⁷ with WHO recommendations added to it. The division of criteria into major and minor has no correlation with the frequency, severity or prognosis of the disease process. The term 'major' only relates to the diagnostic importance. In developing countries where Erythema marginatum is practically never seen due to the complexion and where polyarthralgia is common it is recommended that polyarthralgia be taken as a major criteria with evidence of preceding streptococcal infection and raised ESR if other causes of polyarthralgia can be ruled out, to avoid underdiagnosis of Rheumatic fever. The diagnosis of Rheumatic fever requires the presence of 2 major or 1 major and 2 minor criteria with supporting evidence of antecedent group A Streptococcal infection taken as essential criteria (1992).

Major Criteria:

1. Carditis.
2. Polyarthrititis.
3. Chorea.
4. Erythema marginatum.
5. Subcutaneous nodules.

Minor Criteria:**Clinical Features:** Arthralgia, Fever**Laboratory Features:** Elevated acute phase reactants, Erythrocyte sedimentation rate, C-reactive protein, Prolonged PR interval.**Supporting Evidence of Antecedent Group A Streptococcal Infection:**

- Positive throat culture or rapid streptococcal antigen test.
- Elevated or increasing streptococcal antibody titer.

In 1988 W.H.O has made certain recommendations wherein three special categories in which diagnosis of Rheumatic fever is accepted without 2 major or one major and 2 minor criteria. These are (1) Chorea (2) insidious / late onset carditis with no other explanation (3) Rheumatic recurrence. For (1) and (2) evidence of Streptococcal infection is not required with 'Chorea' being a diagnosis of exclusion. In patients with documented Rheumatic heart disease, the presence of one criterion as of fever, Arthralgia or elevated acute phase reactants suggests presumptive diagnosis of recurrence with evidence of previous Streptococcal infection.

If arthritis is taken as major criteria, Arthralgia should not be taken as minor criteria and if carditis is taken as major criterion, prolonged P-R interval should not be taken as minor criterion. In areas of the world where Acute Rheumatic fever is common, strict adherence to revised Jones criteria may lead to under diagnosis. Though laboratory evidence of Streptococcal infection has often disappeared, other evidence of Rheumatic activity like raised ESR, positive CRP or raised ASO titres or associated carditis or later development of mitral stenosis attests to its rheumatic nature.

Laboratory Findings^{8, 9}: They are not specific for Rheumatic fever. They are helpful in evaluating the activity of Rheumatic fever, and for following course of the disease and in confirming the presence of preceding streptococcal disease.

Hematological Manifestions: Normocytic normochromic anaemia of chronic inflammation is seen. Anaemia is a good index of severity of rheumatic activity and is corrected by suppression of inflammation.

Erythrocyte Sedimentation Rate (ESR): It is an acute phase reactant, used as a minor criterion for diagnosis of Acute Rheumatic fever.

Almost always elevated except in cases of chorea. Though congestive heart failure decreases the rise in ESR due to decreased fibrinogen production, ESR is never normal in the presence of ongoing rheumatic activity. ESR is modified by other factors like anaemia etc. Fall in ESR following cessation of rheumatic activity is slow and so it is not very useful in following the activity of the disease.

'C' REACTIVE PROTEIN: It is an acute phase reactant and abnormal protein (β -globulin) that precipitates with the somatic 'c' – antigen of pneumococci. 'c' stands for 'Capsular carbohydrate moiety of pneumococci. Its apparent antibody – like relation to C-antigen of pneumococcus is only fortuitous (happening by chance). It is not an antibody produced as a result of pneumococcal

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infection. It is synthesized mainly in the liver. CRP return to normal in 2 –3 weeks. CRP is elevated in all cases of congestive heart failure of any etiology but a negative CRP response excludes rheumatic activity and infection as cause of congestive heart failure.

Throat/nasal swabs for culture¹⁰: These are negative in 2/3rd patients due to elimination of organism by body defence mechanism during the period of latency. So assays for streptococcal antibodies is a more reliable method.

Serological Tests: (ASO, Antistreptokinase, Antihyaluronidase, Anti DNAase B, Anti NDAase) Most of these tests assay for neutralizing antibodies to streptococcal extra cellular enzymes. First the test was described by Todd in 1932 determines the titre of antibodies that neutralize Streptolys in 'O'. ASO is still the most standardized and universally used test. A titre of 333 todd units/ml or rising titre is essential or 400 IU/ml and above. ASO titre is positive in 80-85% cases only. When elevated ASO titres along with other enzymes such as anti DNA se-B and anti hyaluronidase are considered in combination the sensitivity is increased upto 90-95%. ASO peaks 3-4 weeks after infection and this peak is maintained for 3 months with slow fall to normal levels in 8 – 9 months. Anti DNA ase peaks at 6 – 8 weeks. The severity of Acute Rheumatic fever has no relation to the antibody response.

Streptococcal Antibody Tests: Streptozyme test is an agglutination test to several antigens which is easy to perform but there is the question of reproducibility and reliability of this test. A titre of more than 200 units is taken as positive.

Chest X-ray:- To assess cardiac size serial X-rays are more useful. Rapid increase in size or 'water flask silhouette' suggests pericardial effusion. Pulmonary edema and congestive heart failure may be suggested by 'Butterfly pattern' on chest X-ray. Diffuse bilateral basal infiltrates may suggests Rheumatic pneumonia. Enlarged left atrial appendage is suggestive of mitral valvular disease in Chronic Rheumatic heart disease.

Electrocardiography (E.C.G): No characteristic pattern. Diagnosis should never be made on E.C.G. findings alone. Prolonged PR interval is also a non-diagnostic criterion since it can get prolonged in many infections. It is also not diagnostic of carditis. Second and third degree heart blocks can occur. Complete atrioventricular block is extremely rare as a manifestation of Acute Rheumatic fever. Prolonged QTc (corrected QT interval) may suggestive of myocarditis.

Echocardiography (2D ECHO)^{11,12,13}: For the first time, the role of Echocardiography was discussed in the latest revision of Jones criteria by American Heart Association (1992) for the diagnosis of Acute Rheumatic fever. These guidelines also highlighted a sub group of "Exception to Jones criteria" in which a diagnosis of Rheumatic fever can be made without strictly following the Jones criteria. These were patients with chorea, indolent carditis and those with a previous history of Rheumatic fever or Rheumatic heart disease. The diagnosis of carditis in Rheumatic fever is usually based on the presence of significant murmurs.

It is well established that Doppler Echo is more sensitive in picking up minor degrees of valvular regurgitation than clinical examination. However, according to the proceedings of the Jones

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criteria workshop published in 1992, there are insufficient data to support a revision of the Jones criteria and reaffirmed the guidelines iterated in the 1992 statement.

In the absence of a “gold standard” for the diagnosis of Rheumatic fever, no single specific laboratory test exists that is pathognomic of Acute Rheumatic fever or its recurrences. At present, Doppler Echocardiography should be used as an adjunctive technique to confirm clinical findings and to evaluate chamber sizes, ventricular function, degree of valvular regurgitation, and morphological features of the valves. It should not be used as a major criterion for establishing the diagnosis of carditis associated with Acute Rheumatic fever in the absence of clinical findings. It is hoped that future refinements of Doppler Echocardiography and prospective studies of its predictive value will prompt reassessment of its role in the diagnosis of Acute Rheumatic fever.

AIMS & OBJECTIVES: To evaluate the risk factors and laboratory profile of “ ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE” in Children under 15 years age group presenting to King George Hospital.

METHODS OF STUDY: Children of age group less than 15years, diagnosed as Rheumatic fever and Rheumatic heart disease both in inpatients of paediatric wards, as well as those who are attending the Outpatient Department in King George Hospital for a period of 2 years (i.e. from July 2004 to June 2006) are included in the study with respect to the following.

1. Risk factors evaluation with respect to economic status, rural / urban community status and overcrowding etc.
2. Laboratory investigations like Hematological parameters, serological tests, E.C.G. Chest X-Ray and,
3. Echocardiographic Evaluation.

MATERIAL AND METHODS: Thirty six cases of Acute Rheumatic fever, which includes eight cases of first attack and twenty eight cases of reactivation of Rheumatic fever were studied during the period 2004-2006 from paediatric medical wards, King George Hospital, Visakhapatnam. The revised (1992) modified Jones criteria with the 1988 WHO modification was taken as a criterion to diagnose Acute Rheumatic fever.

A detailed history was obtained regarding the socioeconomic status, overcrowding, place of residence, family history, exact mode of onset, presenting complaints and treatment received prior to hospital admission. A thorough physical examination was done and the presence and severity of cardiac involvement was ascertained on the basis of physical findings, Roentgenographic, Electrocardiographic and Echocardiographic data.

The following laboratory investigations were done in all cases.

Hb%, T.C., D.C., E.S.R., Peripheral smear examination, Estimation of CRP, Estimation of ASO titre, Throat swab culture / sensitivity, Blood culture, sensitivity Urine: (Albumin, Sugar Microscopy, Culture & Sensitivity), Chest X_Ray, E.C.G, Echocardiography.

Estimation of streptococcal antibodies other than ASO titres could not be undertaken due to lack of facilities and in case of vague clinical manifestations, a repeat ASO titre was done to demonstrate a two –fold rise in titre or persistent elevation of ASO titre. Both ESR and CRP were used

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to follow the course of the disease as negative CRP was considered a better indicator of cessation of Rheumatic activity, while ESR remained persistently elevated for a longer time due to anaemia etc.

Patient diagnosed as having Acute Rheumatic fever were put on Benzathine penicillin prophylaxis 1.2 million units 3 weekly intramuscular injection and followed for a period of 1-2 years for recurrence.

RESULTS:

Risk Factors	Number of Cases	% Cases
Low socio – economic status	36	100
Overcrowding	36	100
Urban community	3	8.3
Rural community	33	91.7

TABLE I: RISK FACTORS FOR RHEUMATIC FEVER

This study shows that all the cases belonged to low socioeconomic status and overcrowding was noted in all cases. Rural predilection (91.7%) was noted.

INVESTIGATION	First attack cases (n=8)		Reactivation cases (n=28)		First Attack and reactivation cases included (n=36)	
	Number of cases	%	Number of cases	%	Number of cases	%
Anaemia	5	62.5	27	96.42	32	88.89
Polymorphonuclear leucocytosis	1	12.5	6	21.42	7	19.44
CRP	8	100	23	82.14	31	86.11
ESR > 20 mm in 1 st hour	7	87.5	10	35.71	17	47.22
Throat swab culture positive for hemolytic streptococcus	-	-	-	-	-	-
ASO more than 400 IU/ml	6	75	19	67.85	25	69.44
Cardiomegaly on chest X-ray	2	25	25	89.28	27	75
P_R prolongation >0.16 sec.	2	25	-	-	2	5.6
Echo cardiographic evidence of Carditis i.e., evidence of Mitral regurgitation and or other valvular abnormalities.	8	100	28	100	38	100

TABLE II: LABORATORY PROFILE OF ACUTE RHEUMATIC FEVER

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Anaemia was noted in 88.89% (32 cases) (i.e., 62.5% and 96.42% of first attack and reactivation cases respectively). Both Rheumatic activity and nutritional deficiency have played a role in producing it. Most of these children were coming from a low socioeconomic status and were malnourished. ESR was positive in nearly 47.22% of the total cases and a high ESR of more than 50mm in 1st hour was noted in nearly (i.e. 87.5% and 35.71% of first attack and reactivation cases respectively). 'C' reactive protein was found to be positive in all first attack cases. Whereas positive in 82.14% of reactivation cases.

Throat swab culture was negative for Group A Beta- Haemolytic streptococci in all cases as patients have come late in the course of the disease, by which time infection may have cleared or culture made difficult by use of antibiotics. Throat swab culture/ sensitivity positivity was noted for pneumococci / staphylococci in 16.66% cases, probably due to frequent contamination. Where as in other studies throat swab culture/ sensitivity positivity was noted in 25-40% cases. ASO titres proved to be very useful in providing evidence for streptococcal infection. 69.44% of total patients (25 out of 36) having titres >400 IU/ml measured by latex agglutination method and in suspicious cases the titres were persistently raised though a twofold rise in titre could not be demonstrated. Cardiomegaly on chest X-Ray was noted in 25% first attack cases where as 89.28% of reactivation cases. While prolonged P_R interval was noted in 25% cases as against 60_70% according to text book teaching.

Risk factor	Nair et al¹⁴ (1990)	Wald et al¹⁵ Pittsburg Study(1985-86)	Present Study (2004-06)
Low socio – economic status	57%	No information available	100%
Overcrowding	47%	-do-	100%
Rural community	-	75%	91.7%
Urban community	-	25%	8.3%

TABLE III : RISK FACTORS FOR ACUTE RHEUMATIC FEVER & REACTIVATION CASES OF CHRONIC RHEUMATIC HEART DISEASE

The present study shows low socio-economic status and overcrowding factors in all the cases.

These two risk factors go hand – in – hand in developing countries and it is this group of people who are likely to have large families living under unhygienic conditions with little or no medical care and hence the high risk of acquiring repeated Streptococcal infections and so the increased risk for Acute Rheumatic fever. In Nair et al study¹⁴ low socioeconomic status was seen in 57% of cases and overcrowding in 47% cases.

Rural preponderance was noted in 91.7% of cases in the present study as Wald et al Pittsburg study¹⁵ noted rural preponderance (75%).

	Nair et al (1990) (n=120)	Present study (2004-06) (n=36)
	%	%
Anaemia	77	88.89
Leucocytosis	55	19.44
E.S.R more than 20 mm in 1 st hour	36	47.22
C.R.P. positive	No information	86.11
Throat culture/sensitivity positive for Beta hemolytic streptococcus	12	-
A.S.O.>400 IU/ml	85.7	69.44
Chest X_Ray showing cardiomegaly	45	75
P_R Prolongation	24.56	5.6
Echo cardiographic evidence of Carditis i.e., evidence of Mitral regurgitation and or other valvular abnormalities.	100	100

TABLE IV: COMPARATIVE STUDY OF LABORATORY
PROFILE OF RHEUMATIC FEVER

Anaemia is noted to be more common in the present study (88.89%) compared to Nair et al study (77%) probably due to superadded factors like nutritional inadequacy and worm infestation. Significant rise in ESR was noted in both the studies. Nair et al showing raised E.S.R. in 36% of cases and present study 47.22% of patients had raise in ESR. Throat cultures were negative in all cases in the present study compared to Nair et al study (12%) cases, probably because of coming to hospital late in the course of the disease and use of multiple antibiotics prior to coming to the institution, so that isolation becomes very difficult. In the present study ASO titre more than 400 IU/ml was noted in 69.44% cases. As facilities for estimation of other streptococcal antibodies were not available, it could not be taken up. Cardiomegaly was seen in 75% of cases in the present study while Nair et al study showed 45%. Probably because the carditis was usually of a severe variety in the present study. P_R prolongation was observed in 24.56% in Nair et al study and 5.6 % in the present study.

RESULTS: Risk factors like low socio-economic status and overcrowding were rampant [100%] and rural predilection (91.7%) was noted. This study has proved anemia (88.89%), elevated ESR (47.2%) positive CRP (86.11%) and ASO titer more than 400 IU/ml (69.44%) are the frequent laboratory abnormalities among the children with Acute Rheumatic fever / Rheumatic heart disease. A routine use of Echocardiography and Doppler studies in all cases of Acute Rheumatic fever and reactivation cases of Chronic Rheumatic Heart disease had helped to detect mild carditis (MR) and mild AR which went undetected clinically.

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CONCLUSION: There is no single symptom, sign or laboratory test that is diagnostic of Acute Rheumatic fever / Rheumatic heart disease. Revised, edited and updated Jones criteria are guidelines to assist practitioners and are not a substitute for clinical judgment. The main concern in liberalizing these criteria in developed countries may be over diagnosis of Acute Rheumatic fever. In developing countries, however, following Jones criteria strictly may result in under diagnosis of this disease.

This study once again throws light on the fact that Rheumatic fever continues to plague the Indian sub-continent mainly the rural population as well as lower socio economic group and unless some long term and objective policy is taken up by the Government, it is likely to place a heavy load on finances and time of health professionals and hence the need to consider the recommendations of WHO regarding the setting of Rheumatic heart clinics in main teaching hospitals with all necessary facilities so as to reduce the morbidity and mortality of the disease.

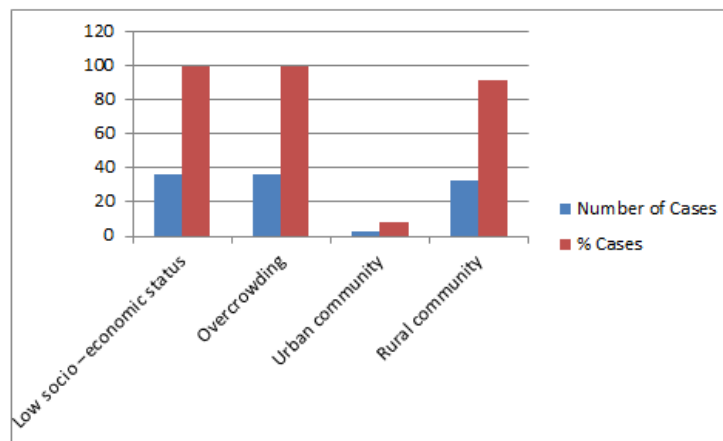


Fig. 1: Risk Factors For Rheumatic Fever (n=36)

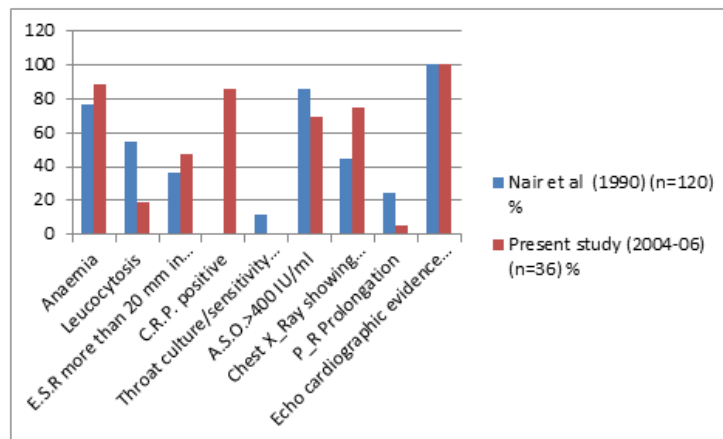


Fig. 2: Comparative Study of Laboratory Profile of Rheumatic Fever

Comparative Study of Risk Factors:

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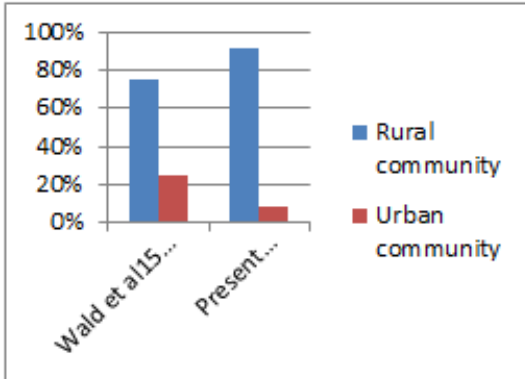


Fig. 3

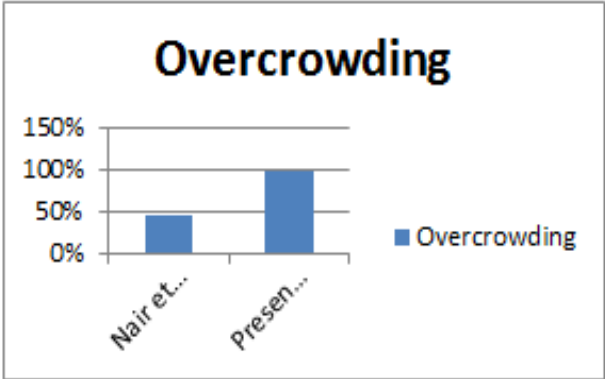


Fig. 4

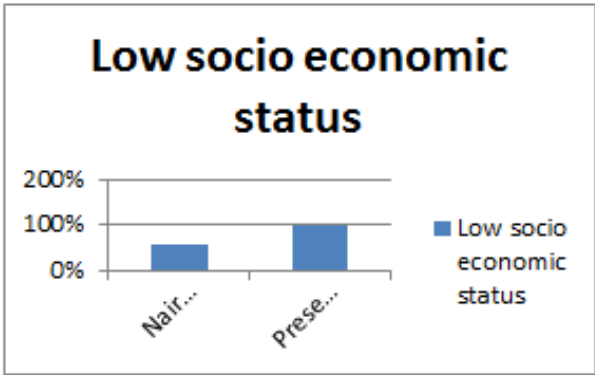


Fig. 5

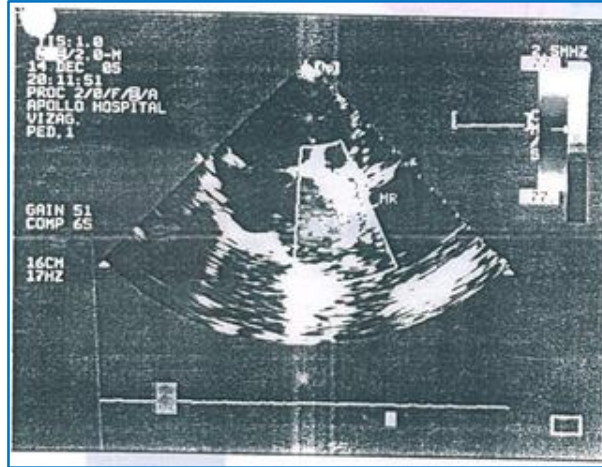
C - X Ray PA VIEW NORMAL S TUDY:



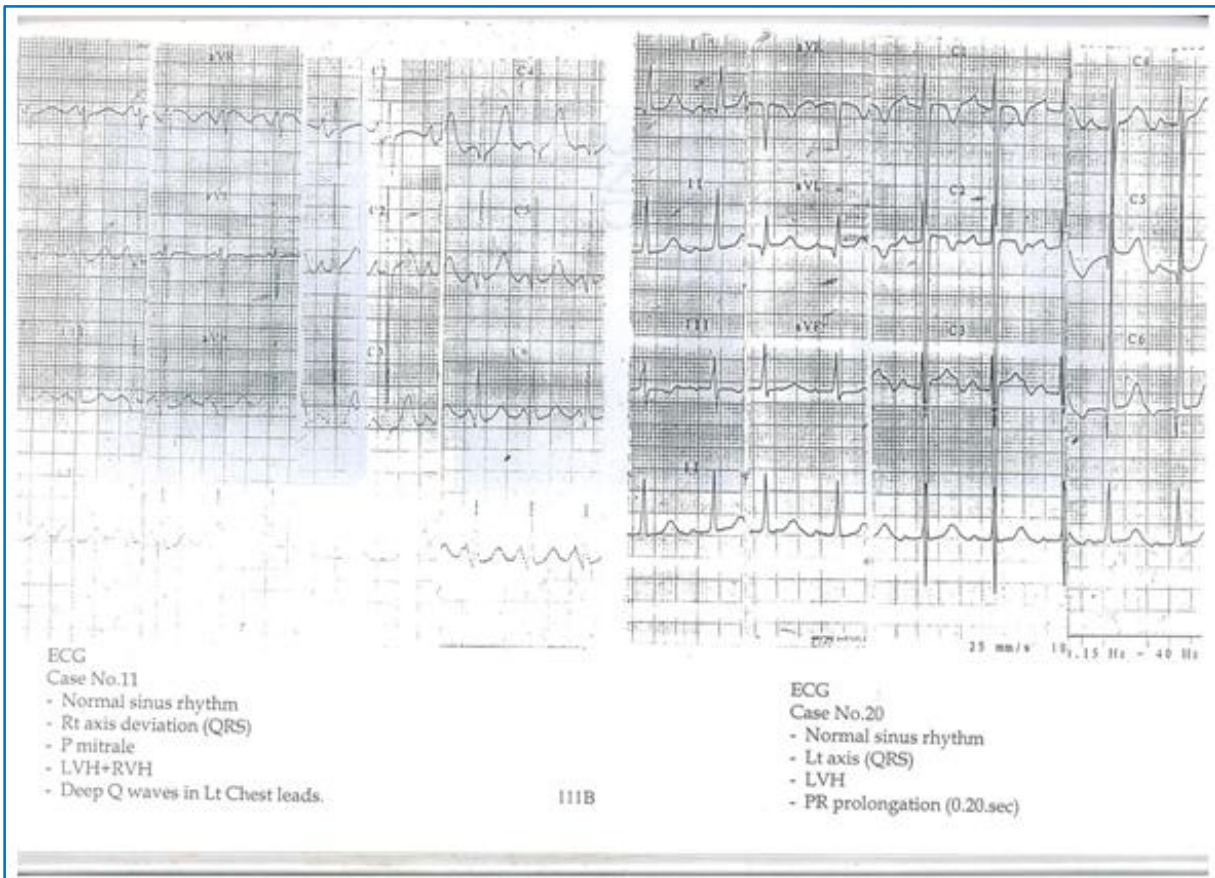
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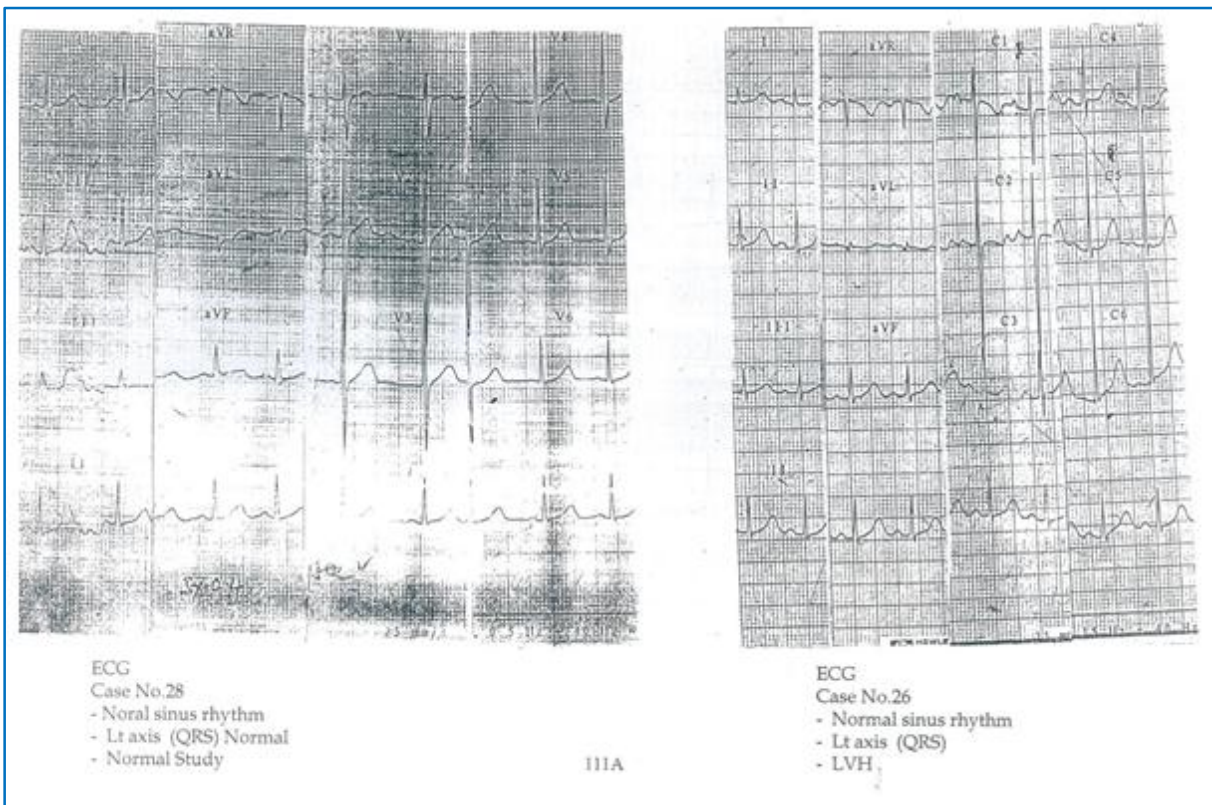
C - X Ray PA VIEW GROSS CARDIOMEGALY BIVENTRICULAR HYPERTROPHY:

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2D- ECHO: Parasternal long axis view. Showing Severe mitral regurgitation.



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