THE TURKISH JOURNAL OF PEDIATRICS

VOLUME: 31 NUMBER: 3 JULY - SEPTEMBER 1989

A Joint publication of the Turkish National Pediatric Society and the Turkish and International Children's Center

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This Journal is listed in *Current Contents, Index Medicus, Abstracts on Hygiene and Communicable Diseases, Tropical Diseases Bulletin* and the CAB Abstracts database.

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The Turkish Journal of Pediatrics 31:185 - 199, 1989

LONG-TERM PROGNOSIS OF RHEUMATIC MITRAL REGURGITATION: PRESENTATION OF YEARLY PROGNOSTIC REGRESSIONS IN RELATION TO AFFECTING FACTORS*

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Key words: acute rheumatic fever, mitral regurgitation, penicillin prophylaxis, cardiothoracic ratio, electrocardiogram

Studies have shown that the short or long-term results of the incidence of residual heart disease in acute rheumatic fever depend on the severity of the carditis, on the number of recurrences[1-6], on the duration of the pretreatment interval[2-10], which is debatable, and on the use of larger and longer doses of anti-inflammatory agents[9-10]. Therefore, in order to establish a more accurate prognosis, it is necessary to classify each individual case in relation to the factors that influence the prognosis of rheumatic fever.

The striking differences in the course and prognosis of this disease before[11-13] and after the penicillin era[1,2,4,14] show the importance of the beneficial effect of penicillin in treatment and in prophylaxis of recurrences[14-17]. Many studies have also shown that the degree of heart involvement is of importance[3-6,12,16,18].

Mitral regurgitation (MR), which is the most frequent manifestation of rheumatic heart disease[1,4-6], was found in 92% of our 144 patients with carditis[19]. Since pericardial involvement does not leave sequelae, the clinician is interested in the prognosis of the valvular lesion, and especially of the mitral regurgitation[5].

A clinical, objective, quantitative classification is needed which shows the severity of regurgitation. The well-known and established studies have used the following three criteria as a classification system which has to be revised since it may lead to errors or ambiguities: 1) Presence of congestive heart failure and/or pericarditis[1]; 2) Intensity of the apical systolic murmur as an index of the degree of MR[16,17,20]; 3) Electrocardiographic or radiologic criteria for the estimation of cardiac enlargement[1,21].

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In our experience, we encountered the following drawbacks in these criteria: 1) Rheumatic pericarditis has an excellent prognosis, while congestive heart failure has a poor prognosis. Thus, consideration of both in the same prognostic criterion is ambiguous. 2) Intensity of the apical systolic murmur does not correlate well with the grade of severity of MR, hence it is a poor index; 3) At the onset of carditis there is often a mild, pericardial effusion, which may at the start be clinically latent, but can be recognized by serial follow-up of the increase in the electrocardiographic voltage and by the simultaneous decrease in the cardiothoracic ratio on the chest X-ray or by echocardiography. The effusion leads to a false negative evaluation of the electrocardiographic and a false positive estimation of the radiographic left ventricular enlargement, which are clinical indices of the grade of severity of MR.

Another factor which greatly influences the degree of heart size is the respiratory phase[22]. An X-ray taken on expiration can show a false positive grade III enlargement, straight left cardiac border, and congestion in the lung fields in a normal individual[22].

After considering all the disadvantages of the afore-mentioned criteria, we decided to use other criteria for estimating the degree of MR. From the follow-up data, regressions were developed to estimate the yearly rate of disappearance of MR according to a classification system based on promptness of treatment, continuous or irregular prophylaxis, presence or absence of congestive heart failure, and grade of severity of MR. The method of estimating the latter yields considerably less false positive or false negative results, and is objective, since it is based on quantitative measurements. The results of 117 children with MR who were followed-up at a median 10 years (1028 patient years) were evaluated and those pertaining to 86 patients with isolated mitral regurgitation are presented in this paper.

Material and Methods

The material consisted of 117 children with an initial attack of MR due to rheumatic fever who were hospitalized in the Pediatric Cardiology Department of Cerrahpaşa Medical Faculty, between 1964-1983, and whose laboratory studies were complete with respect to the methodologies presented. They were followed up for 2-21 years by the same experienced pediatric cardiologist (T.O.), who was familiar with the results of earlier reports and had prospectively planned the follow-up in the Outpatient Clinic of the Division.

The course and prognosis of the condition were evaluated with respect to: 1) pretreatment interval; 2) strict compliance with penicillin prophylaxis; 3) presence of congestive heart failure; 4) degree of severity of MR.

1) The pretreatment interval was the time that had elapsed between the onset of symptoms attributed to acute rheumatic fever and the initiation of the antiinflammatory therapy. If proper therapy was instituted more than three weeks after the onset of the initial symptoms, these patients were classified as "late" in contrast to the "early" group. Proper treatment consisted of 800,000 U of a daily dose of penicillin for ten days, and 2 mg/kg/day of prednisone and 0.1 g/kg/day of aspirin for three weeks which was followed by a gradual reduction of doses for another six weeks. In our clinic, however, all patients with active carditis receive corticosteroid treatment with a weekly monitoring of the sedimentation rate.

2) Penicillin prophylaxis was started on the 11th day with the administration of 1,200,000 U benzathine penicillin. Those who received the drug every three to four weeks without fail were classed as the regular prophylaxis group while those who missed doses for a few months or a longer period but had later continued the drug on a regular basis were classed as the irregular prophylaxis group.

3) Patients with carditis were considered to have congestive heart failure if dyspnea not due to a respiratory infection was present and if enlargement of the heart was not due to pericarditis. Thus, the most common false positive diagnosis of congestive heart failure were avoided.

4) The presence and grade of severity of mitral regurgitation (MR): A persistent pansystolic murmur, maximum at the apex of grade II-IV intensity, which was transmitted towards the axilla during the hospitalization period of three to six weeks was accepted as MR in the presence of other major or minor criteria of acute rheumatic fever[23].

The degree of severity of mitral regurgitation can be assessed from the cardiothoracic ratio, as well as from electrocardiographic voltage-dependent criteria of left ventricular enlargement[24]. Simultaneous use of both methods reduces fallacies of either system, but still has the following drawbacks which have been corrected accordingly:

The cardiothoracic ratio is very highly correlated with the respiratory phase[22]. A right diaphragmatic level of one intercostal space higher in the same individual leads to a mean increase of 7% in the cardiothoracic ratio. In comparison with the values in the same subject and also the classification of cardiac enlargement values, a correction was made according to Onat[22], which was designed to standardize all cardiothoracic ratio values to a right diaphragmatic arc's level of under the fifth anterior rib. This was referred to as the corrected cardiothoracic ratio.

In the acute phase of carditis about 13% of our cases manifested pericarditis clinically but in another 16% pericarditis was diagnosed by a significant increase in the voltage of various standard as well as unipolar chest leads with a

simultaneous decrease in the corrected cardiothoracic ratio within one or two weeks. In order to correct the false positive heart enlargement on the chest X-ray due to pericarditis, the values used were those which had been obtained after a serial clinical detection of pericarditis and not those which had been taken at the inital examination. In later years of the study, where echocardiography was used, the above-mentioned serial clinical detection and echocardiographic findings of pericarditis were in conformity.

With these above-mentioned points in mind, the grading of mitral regurgitation was considered IA if the diaphragm-dependent corrected cardiothroracic ratio on the postero-anterior chest teleradiography was $\leq$ 0.50, R-wave in V5 was less than 2.5 mV, R in V5 + S in V1 was less than 3.5 mV, and if no third heart sound could be heard at the apex. It was subgrouped as IB, if S3 was audible but the above-mentioned criteria for left ventricular enlargement were absent. A grade II was designated, if the cardiothoracic ratio was between 0.51-0.55 and either RV5 + SVI was 3.5 mV or RV5 was >2.5 mV, or if the corrected cardiothoracic ratio was near 0.50 but RV5 + SVI was over 4.5 mV. Grade III regurgitation was designated if the corrected cardiothoracic ratio was $\geq$ 0.56 and electrocardiographic signs of left ventricular enlargement accompanied it. A distribution of patients in the specified subgroups of this classification system according to age and sex is presented in Table I.

Sixty-eight patients from the initial 117 with MR were followed-up for 10 years or longer. MR was the only valvular involvement in 86 patients; aortic regurgitation accompanied the mitral regurgitation in the remaining 31 patients. In this study, prognosis was based on the traced 730 patient-years of the 86 initally isolated MR patients. The mean follow-up of these subjects was 8.49 years, while the median value was over ten years.

The patients were examined daily in the first three or four weeks, weekly in the second month and in the tenth week, which usually corresponded to a week after the completion of the corticosteroid treatment. The examinations continued at three monthly intervals in the first year, and at six monthly intervals later on, where all pertinent data were checked within a prospective plan.

The distribution of the missing data of the patients lost to study in a longitudinal study can lead to biased results if significantly different from the remaining subjects. Therefore, a Chi square test was used to assess the evaluations of these patients in different years in relation to the following factors: degree of severity of MR ($X^2 = 1.236$; $p > 0.30$), percentage of patients with congestive heart failure ($X^2 = 0.401$; $p > 0.50$), pretreatment interval ($X^2 = 0.108$; $p > 0.70$); percentage of those with regular penicillin prophylaxis ($X^2 = 0.037$; $p > 0.80$). The values of those lost to study were not statistically significantly different from the

TABLE I: Distribution of Patients in the Classification System According to Age and Sex

MR°	Prophylaxis	Onset of Therapy Early	Onset of Therapy Late	CHF *	Sex Male	Sex Female	Age (Yrs) Mean ± SD
IA	P ±	2	5	0	1	6	9.65 ± 2.81
	P +	9	3	0	6	6	
IB	P ±	5	2	0	4	3	9.43 ± 2.67
	P +	10	4	0	6	8	
II	P ±	7	7	6	5	9	9.57 ± 2.64
	P +	13	9	2	10	12	
III	P ±	2	3	5	1	4	9.42 ± 3.19
	P +	2	3	4	3	2	
Total	P ±	16	17	11	11	22	9.54 ± 2.71
	P +	34	19	6	25	28	range 4-14
		50	36	17	36	50	

* MR° = grade of severity of mitral regurgitation
CHF = congestive heart failure
P ± = irregular penicillin prophylaxis
P + = regular penicillin prophylaxis

distribution of the total initial material. Thus, the yearly percentage of patients with disappearance of MR was accepted to represent unbiased data.

The yearly linear regressions of the disappearance rate of MR were calculated from the yearly percentage of patients without regurgitation/total MR present for that follow-up year. The two patients who died from carditis were considered persistent carditis in the following years. The results pertaining to multiple factors influencing the disappearance of regurgitation represent the basis for the study.

The MR was considered cured, if the apical systolic murmur had disappeared and was also undetectable after exercise on subsequent visits, and if there were no electrocardiographic or radiologic signs of left ventricular enlargement.

Results

The age at onset of MR was 9.54 years with a range from 4.4 to 14.0 years. This did not differ significantly in groups of severity of MR. Female preponderance in general (58.1%) as well as in relation to groups of grade of severity of regurgitation was not significant ($p > 0.20$) nor were sex differences in relation to regularity of penicillin prophylaxis ($X^2 = 1.802$; $p > 0.20$).

Obtaining treatment late was not significantly associated with regularity in prophylaxis. The incidence of patients with continuous penicillin prophylaxis was

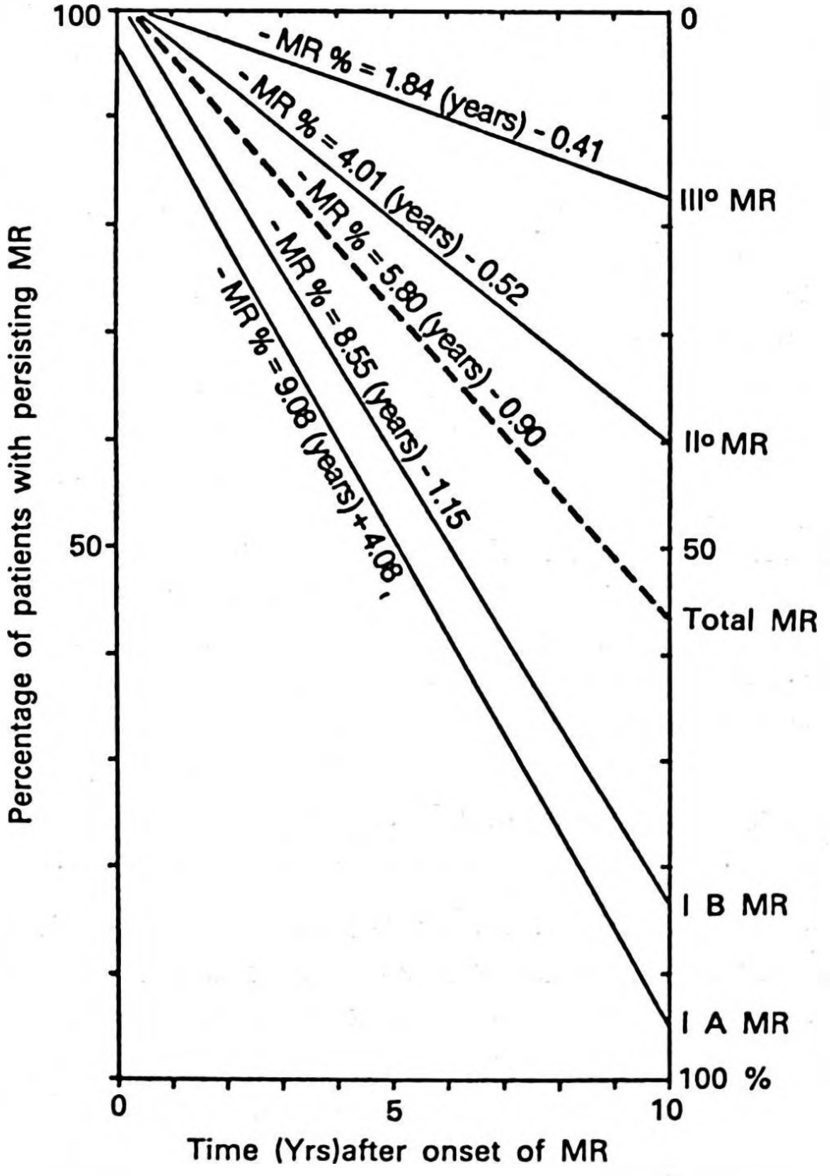

Fig. 1: Percentage of patients with persisting mitral regurgitation (MR) in relation to time (yrs) after onset of MR. The regression equations are presented in percentage of disappearance of MR (−MR%), and their slopes represent the yearly probability (%) of disappearance of MR, which increases with decreasing grade of severity of MR. Note that the patients without cardiac enlargement but with a third heart sound at onset (IB) have practically the same slope as IA, but are a year late to recover.

TABLE II: Linear Regressions of Percentage of Yearly Disappearance of Mitral Regurgitation (MR) in Relation to Its Grade of Severity and to Subgroups of Penicillin Prophylaxis and Time of Onset of Treatment

Grade of Severity of MR	n	Regressions of Yearly % Disappearance of MR
Grade I	40	9.06 (years) − 3.15
PP irregular	14	6.57 (years) − 9.55
PP regular	26	10.26 (years) + 0.54
PP regular + Early*	19	13.29 (years) + 1.58
Grade II	36	4.01 (years) − 0.52
PP irregular	14	1.46 (years) + 0.67
PP regular	22	5.60 (years) − 1.10
PP regular + Early	13	7.01 (years) − 3.89
PP regular + Late*	9	3.94 (years) + 2.10
Grade III	10	1.84 (years) − 0.41
Congestive HF*	17	3.12 (years) − 2.11
Congestive HF + Early	9	3.55 (years) − 6.56
MR (Total)	86	5.80 (years) − 0.90
MR + Early	50	7.11 (years) + 2.69
MR + Late	36	4.26 (years) − 5.85
MR + regular PP*	53	7.31 (years) + 0.36
MR + irregular PP	33	3.18 (years) − 3.18
MR + reg. PP + Early	34	8.92 (years) + 3.27
MR + irreg. PP + Late	17	3.54 (years) − 7.74
MR + irreg. PP + Early	16	2.78 (years) + 2.13
MR + reg. PP + Late	19	4.87 (years) − 4.18

*Early = pretreatment interval less than three weeks
Late = pretreatment interval more than three weeks
PP = penicillin prophylaxis, HF = heart failure

68% in those with a pretreatment interval of less than three weeks in contrast to 53% in those with a pretreatment interval of more than three weeks ($X^2 = 1.458$; $p > 0.20$). However, there was a significant tendency for those patients with congestive heart failure at onset to continue prophylaxis irregularly ($X^2 = 4.903$; $p < 0.05$).

The mean severity grade of MR was 1.59 in those with a short pretreatment interval as compared to 1.79 (grades I-III) in the group with a pretreatment interval

exceeding three weeks. Likewise, 65% of those without cardiomegaly and 52% of those with cardiomegaly (groups II-III) were in the early treated group. The difference was not statistically significant ($X^2 = 0.967$; $p > 0.30$). The incidence of regularity in prophylaxis was not significantly different in the three groups of severity of MR ($X^2 = 1.252$; $p < 0.20$).

Linear regressions estimating the percentage of the yearly disappearance of MR in relation to its grade of severity, subgroups of penicillin prophylaxis and time of onset of treatment are presented in Table II. Of the 86 patients with pure MR, the yearly probability of disappearance of regurgitation was 5.8% (Table II; Fig. 1). The expected median time of disappearance was 8.8 years. This general tendency to recover is modified very significantly in relation to grade of severity of MR. It decreased to 1.84% per year in grade III regurgitation, and to 4.01% per year in grade II regurgitation, but increased to 9.06% per year in grade I regurgitation (Table II). A 50% chance of recovery is expected within 5.8 years in group I (A+B), while it is only 18% and 40% in 10 years in groups III and II, respectively. The estimated chance of recovery in 10 years, according to the regression is 87% in group I. The real value was 85%.

The effect of strict compliance with penicillin prophylaxis and the pretreatment interval are seen by the differences in the slopes of the regressions in which the grade of severity of regurgitation is being held constant (Table II; Figs. 2, 3). In patients with grade I regurgitation, the yearly chance of recovery was 10.26% vs. 6.57% in those with regular and irregular prophylaxis, respectively (Table II; Fig. 2). The same tendency of differences are observed, but with smaller slopes in patients with grade II regurgitation (Table II; Fig. 3). The yearly probabilities for those with or without prophylaxis are 5.60% vs. 1.46%, respectively; the slope is three times steeper. The differences of 31% vs. 9% in five years, and 46% vs. 13% in ten years were not statistically significant at the 0.05 level because there were few patients in the subgroups. However, this was consistent in all years when grade of severity of regurgitation was held constant in the grade I and grade II groups. The higher rate of disappearance of MR in the regular vs. irregular penicillin prophylaxis in group I was significant in five years and on the borderline in ten years (Fig. 2). The median expected recovery time of MR was 4.9 years vs. 9.06 years in the patients receiving regular or irregular prophylaxis, respectively.

The probability of the disappearance of MR increased with a pretreatment interval of less than three weeks. If prophylaxis was continuous and therapy was started within three weeks, the yearly chance of recovery was 13.3% in grade I and 7% in grade II regurgitation (Table II; Figs 2, 3).

If grade of severity as well as regularity of prophylaxis are held constant, the differences between early and late onset of therapy are still conspicuous, that is,

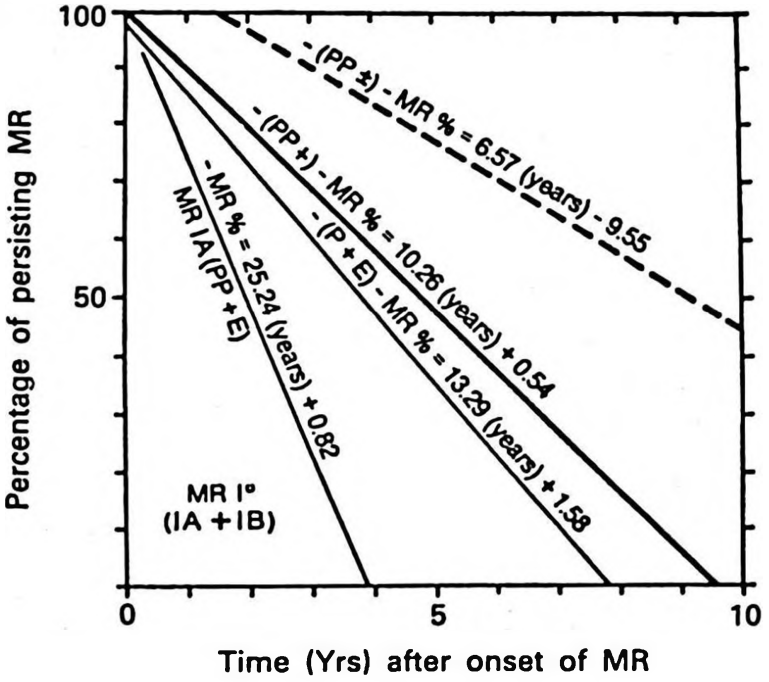

Fig. 2: The regression equations present the yearly probability (%) of disappearance of mitral regurgitation (−MR%) in grade I. The yearly rate of disappearance of MR was 6.57% in patients with irregular penicillin prophylaxis; it increased to 10.26% with regular penicillin prophylaxis to 13.29% if also treated early (E), and to 25.24% if no third sound was heard (IA). Note that all MR I patients with continuous prophylaxis recover, and that it occurs earlier in those patients with a shorter pretreatment interval (E) and in those without an audible third heart sound.

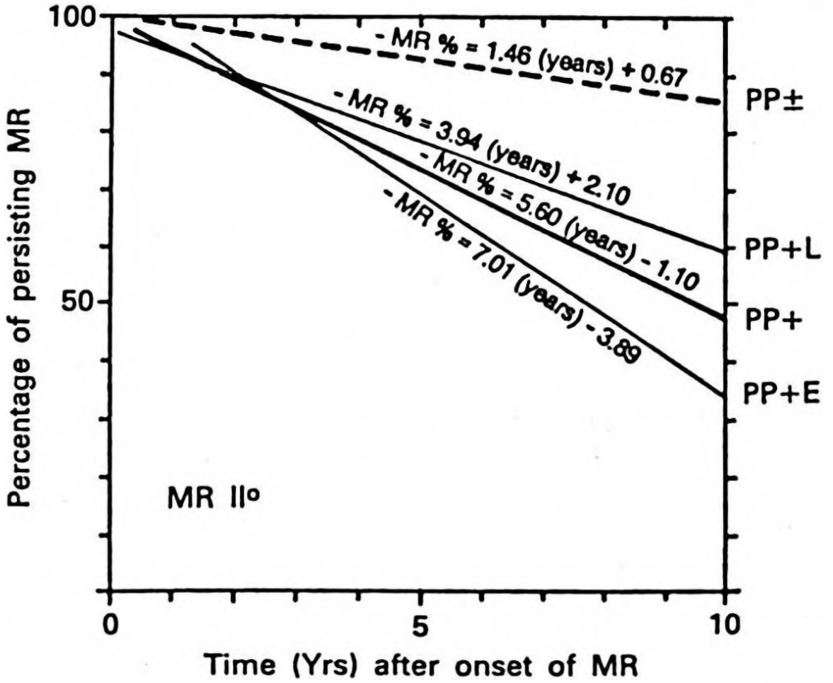

Fig. 3: Same coordinates and abbreviations as in Figs. 1-2, in MR grade II. Note that the rate of disappearance of MR is much lower if penicillin prophylaxis is irregular, and that in the same grade of severity and in continuous penicillin prophylaxis the slope is steeper in earlier onset of therapy (E) as compared to onset of therapy later than three weeks (L).

7% per year as compared to 3.9% per year in grade II. Thus, according to the regressions presented in Table II and Fig. 3, the estimated chance of recovery in group II regurgitation with continuous penicillin prophylaxis is 66% in ten years if the pretreatment interval is less than three weeks while the estimate is reduced to 41% for a longer interval. The actual values were 57% vs. 33%, respectively. The same tendency was observed in group I. The yearly rate increased to 25.2% in group IA, if the patients were treated earlier than three weeks and continued with prophylaxis (Fig. 2). In contrast, the chances were three times less (7.3%), even in group IA, if penicillin prophylaxis was continued irregularly. The same rules were valid for the total group I A+B (Table II).

Table II also presents regressions of yearly chances of recovery of MR in relation to duration of pretreatment interval and to regularity of prophylaxis, but disregards the grade of severity of regurgitation. The yearly chances of recovery from MR were 7.3% vs. 3.2% in patients with regular or irregular penicillin prophylaxis, respectively. The rate of disappearance of MR in five years was 41% vs. 8% with regular vs. irregular prophylaxis, respectively ($X^2 = 7.080$; $p < 0.01$). In ten years the same rate was 67% vs. 28%, respectively ($X^2 = 5.348$; $p < 0.025$).

Congestive heart failure was present in 17 patients (20%). This incidence was 14% in those with a short pretreatment interval in contrast to 28% in those with an interval of more than three weeks. The difference, however, was not significant ($X^2 = 1.712$; $p > 0.10$). Likewise, of the 17 patients with congestive heart failure, seven were treated before and ten after three weeks ($p > 0.30$). The yearly probability of recovery from MR was 3.1% in those with congestive heart failure, but in nine, in which therapy was instituted early, it was 5.55%, with a median recovery time of ten years (Table II).

The course of patients in which, at the last examination, MR had not yet disappeared, but who were followed up for less than ten years was as follows: All seven of group IA remained in group IA, 12 of group IB became group IA; of the 28 patients in group II, 16 regressed to grade I, 10 remained in grade II and two deteriorated to grade III; of the nine patients in group III, two regressed to grade I and two to grade II, while two remained in group III and two died. Thus, of the total 86, there were only four patients in whom the course deteriorated, resulting in the death of two.

Mitral stenosis was observed in four female patients and in one male patient (5.8%), who were in grade III with congestive heart failure and irregular prophylaxis. In the two patients with continuous prophylaxis, the mitral regurgitation had disappeared but mitral stenosis developed at age 20, 6-8 years after the discontinuation of prophylaxis. This led us to change our policy of discontinuing prophylaxis in the third decade even if the mitral regurgitation was seen to have completely disappeared.

The mortality rate in our study was 2.3% (2/86). The two patients who died, one aged 17 and the other aged 15, were both females and displayed all the unfavorable factors in common. They had manifestations of congestive heart failure at onset, were in group III, the pretreatment interval was long, and they did not continue prophylaxis.

Discussion

Our study demonstrates that persisting mitral regurgitation depends on its grade of severity, provided of course that penicillin prophylaxis is continued on a regular basis and on the duration of the pretreatment interval. These points are discussed below comparatively with the findings in published reports. Studied have shown that residual heart disease has increased with recurrences[2-6,11,13,17,25,26], and that it is the continuation of antistreptococcal prophylaxis that has reduced these recurrences, resulting in a higher rate of recovery and also a lower death rate. Tompkins et al[14], have reported that of 79 isolated or combined MR patients, no deaths occurred after the initial attack, provided that penicillin prophylaxis was continuous. This was also observed in our patients.

The recurrence rate/year in our study was 1.25% if penicillin prophylaxis was continuous, while it was 27.2% if it was irregular. Our incidence of recurrence, inspite of the regular use of penicillin was a little higher than the reports of Tompkins et al[14] and Sanyal et al[16], but much lower than other published studies[2,15,17,27].

The favorable results of continuous prophylaxis could substantially be shown in our study by keeping the grade of severity constant (Table II, Figs. 2, 3).

Besides the above-mentioned role of the regularity in penicillin prophylaxis, the incidence of the disappearance of MR was found to be a function of time, as well as grade of severity. Studies reporting the incidence of the disappearance of mitral regurgitation are few-they can be grouped as those presenting yearly results[14], those reporting final results, without specifying the time of disappearance[4,5,13,16], and those presenting results recorded after one, five or ten years[1-3]. Their systems of classification into subgroups, and total time of observation differ, and different criteria have been utilized to estimate the grade of severity of mitral regurgitation.

Tompkins et al[14], were the first, and only investigators, to present yearly incidences of persisting MR, but they did not give yearly results of subgroups, i.e., in grades of severity of regurgitation. They reported the results of their nine-year follow-up study of 79 patients with an initial attack of MR who were kept on continuous penicillin prophylaxis and observed that regurgitation had disappeared in 74% of the cases. This incidence was 36% (5/14) in those with, and 84%

(43/51) in those without cardiomegaly. The same incidence computed from our regressions for nine years of the comparable group with regular prophylaxis would be 93% for grade I, 49% for grade II and 16% for grade III. An average of our grade II and III, i.e., of those with cardiomegaly for nine years is 39%, versus 36% as reported by Tompkins et al[14]. Thus, the regressions presented herein are consistent with the final-results of Tompkins et al[14].

Bland and Jones[13], have reported their results of 87 patients with MR over a twenty-year period. The grade of severity of regurgitation was not mentioned and they represent only a small fraction (87/806) of the original 1000 patients who revealed rheumatic heart disease, 653 at onset and 806 throughout the 20 years. Nevertheless, they represent a time prior to antistreptococcal prophylaxis and show that the regurgitation murmur disappeared in 33%. This natural favorable incidence of disappearance was balanced by the development of mitral stenosis in 27%. The disappearance of MR in ten years in our group with irregular penicillin prophylaxis was 28% which is consistent with the value reported by Bland and Jones[13].

There was a 33% incidence of disappearance of MR in 45 patients in the five-year follow-up study of Sanyal et al[16]. This value decreased to 14% in patients with congestive heart failure. These figures are consistent with our findings and can be predicted from our corresponding subgroup regressions.

The Irvington-on-the-Hudson Study give quite different values in their two reports on the results of patients with MR, although their study population was the same 441 patients with acute rheumatic fever seen from 1950-57. They present an overall disappearance rate of 38% in 61 isolated MR patients for a mean follow-up time of 7.8 years[5], while the rate was 75% in their 59 patients in Table VI[4]. The disappearance of MR in both reports depended on the size of the heart, and on whether there had been previous attacks or not, which are consistent with our findings.

According to the results of a joint report from the United Kingdom and the United States[3], the incidence of disappearance of MR in the same 97 patients studied with no previous heart disease and without "failure and/or pericarditis" was 48%, 67% and 72%, respectively, in one, five and ten years. The differences in the rates of disappearance in ten years in their subgroups of MR were not significant (81%, 73% and 67%, respectively, with increasing severity). This might be due to the method of estimation of the severity of MR which was based on a system graded in relation to the intensity of the apical systolic murmur[1], which is not a good index of severity of MR. It showed great overlapping in our material with the grades of severity of regurgitation presented herein, although differences between both ends were significant at the 0.05 level. Our results in five and ten years correspond to the values given above[3], but the rate of disappearance of

MR in the first year was never that high in any of our groups. Their recovery rate of 11% within ten years, if previous heart disease and congestive heart failure were present, is consistent with our findings in the group with failure in which the onset of therapy started late.

Results of earlier studies regarding the relationship between the pretreatment interval of the initial attack and the incidence of residual heart disease in rheumatic carditis, but disregarding its severity, have shown a higher incidence of disappearance of heart disease in the group with onset of therapy earlier than two weeks. In certain studies the difference was not significant[4,8]. Other workers [3,6,7,9,10,28] have shown a significantly higher incidence of residual heart disease in their groups with a pretreatment interval of more than two weeks. Our compilation of the incidence of residual heart disease in the above-mentioned 856 carditis cases, regardless of their severity and very varied follow-up time (three months to ten years) has, however, revealed a very high X^2 value equal to 37.38, which is in favor of early onset of treatment. The discrepancies in the incidence of residual heart disease were probably due to the differences in the follow-up time, severity of carditis and their criteria for defining the grade of severity.

It is debatable as to whether the above-mentioned beneficial effect on residual heart disease is due to prompt treatment or to a selective association of milder cases in the early treated groups. It is anticipated, but not proven, that with prolongation of the pretreatment interval in carditis, damage to the heart would become more severe. Therefore, we studied this in our material and found no significant relationship between the pretreatment interval and the grade of severity of MR at onset, if three weeks are taken as the criterion ($p > 0.30$). The incidence of congestive heart failure in our series was present in 14% of those with a shorter pretreatment interval in contrast to 27.8% of those with a longer interval. This difference, however, was not significant at the 0.05 level ($X^2 = 1.712$, $p > 0.10$). Thus, it is debatable, whether the pretreatment interval determines the severity of carditis, although there is a tendency towards milder carditis if the pretreatment interval is short.

For a direct solution to the problem, one has to compare the results in the same grade of severity and in the same observation time. Our results in this respect revealed that when severity of MR, which was more strictly defined, was held constant, the disappearance rate/time function was higher in the early treated group (Figs. 2, 3). The same tendency persisted in all the groups, despite the fact that severity of regurgitation was not significantly less in the earlier treated patients. Thus, we can conclude that the beneficial effect of early treatment must be responsible, per se, for lowering the incidence of residual heart disease, provided that penicillin prophylaxis is continued, and the carditis is not very severe, because the tendency of severe carditis disappearing is low (Table II, Fig. I).

It is, however, mainly those patients with a mild to moderate form of carditis, who with early onset of therapy have more favorable short-term results as compared to late onset of therapy. A comparison of only long-term results in mild carditis may obscure the difference in the two pretreatment interval groups, because as it was demonstrated in our patients without cardiac enlargement (grade IA+B), the MR will disappear earlier, if the pretreatment interval is less than three weeks.

Summary

Acute rheumatic isolated mitral regurgitation was followed up in 86 children for 730 patient-years. The grade of severity of regurgitation was classified according to degree of left ventricular enlargement, which was based on an original method of correction of cardiothoracic ratio on the chest x-ray, taking into consideration the diaphragmatic level, and electrocardiographic criteria for age. A combination of both quantitative estimations, after the regression of a detectable pericardial effusion reduced false-positive radiologic and false-negative electrocardiographic results. Linear regressions of percentage of yearly disappearance of MR were presented in relation to the grades of severity; the mean yearly rate of disappearance of 5.8% increased to 9.08% in mild, and decreased to 1.84% in severe regurgitation. The effect of other beneficial factors such as the shortness of the pretreatment interval and regularity of prophylaxis could be demonstrated by keeping the grade of severity of regurgitation constant. Thus, chances for recovery in reported years after onset, up to ten years, can readily be calculated from the presented regressions with regard to the appropriate subgroups.

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The Turkish Journal of Pediatrics 31:201 - 208, 1989

CLINICAL AND IMMUNOLOGICAL EVALUATION OF PATIENTS WITH SELECTIVE IgA DEFICIENCY*

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Key words: selective IgA deficiency, surface immunoglobulins, T cell subsets, cell-mediated immunity

Among the most frequent forms of primary immunodeficiency diseases is that called selective IgA deficiency which is characterized by absence of serum IgA or a serum IgA level of less than 5 mg/dl[1]. In cases with serum IgA levels sharply below the normal values but above 5 mg/dl, partial IgA deficiency should be considered. The etiology of selective IgA deficiency is unclear but it has been assumed that various immunopathogenic mechanisms may cause the disease. In most cases an intrinsic defect in B lymphocytes leads to IgA deficiency[2-4]. However, in some patients the increase in IgA specific suppressor T lymphocyte activity is likely to cause the disease[5,6]. The clinical features of selective IgA deficiency vary greatly, of which chronic recurrent infections, allergic diseases, hematological disorders, gastrointestinal manifestations, autoimmune diseases and malignancies have been frequently observed[7,8].

In this study patients with selective IgA deficiency are evaluated in terms of their clinical findings and T and B cell-mediated immunity.

Material and Methods

Fourteen patients, 12 with selective and two with partial IgA deficiency were included in this study. Thirteen of the patients had been diagnosed during the measurement of the serum immunoglobulin levels of patients who suffered from recurrent infections, allergic disorders or hematological diseases. One patient, the mother of Case 1 (UU), was diagnosed during the family screening of serum IgA levels in seven patients. The patients' ages, with the exception of one (BU), who was 34 years-old, ranged between two-eleven years.

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Immunolgical studies:
Serum immunoglobulins (IgG, IgM, IgA) were determined quantitatively by using immunodiffusion plates (Behring-Werke, W. Germany)[9]. Delayed hypersensitivity skin tests were performed by applying the following antigens in seven patients: PPD (5 U/0.1 ml), phytohemagglutinin (PHA) (10 mg/0.1 ml; Burroughs Wellcome), SK/SD (final concentration 50 U SK, 12.5 U SD/0.1 ml, SK/SD-varidase; Lederle) and *Candida* (1 PNU/0.1 ml; Hollister-Stier). Induration was determined at 48 h. The E-rosette test was performed in all patients using the method described by Jondal et al[10].
In vitro blastogenic response of lymphocytes to PHA was evaluated using a previously described method with some modifications in which the whole blood of 12 patients and 11 age-matched controls was studied[11,12]. The results were expressed as a stimulation index (SI= cpm (count per minute) of stimulated cells/cmp of unstimulated cells). The SI values above 20 were accepted as normal.
Surface immunoglobulin positive B cells were determined by fluorescent conjugated antisera against Ig isotypes (polyvalent, anti-IgG, IgM, IgA sera; Behring Werke, W. Germany) in eight patients and 19 healthy age-matched controls[13].
T lymphocyte subpopulations (Pan T, helper, suppressor T cells) were investigated in seven patients and 19 age-matched healthy controls by using monoclonal antibodies (OKT_3, OKT_4, OKT_8; Behring Werke, W. Germany) and the standard indirect immunofluorescence technique[14].
Anti-nuclear, anti-reticulum, anti-cytoplasmic, anti-parietal cell, anti-smooth muscle, and anti-mitochondrial antibodies were determined in ten patients, utilizing heterologus tissue and the indirect immunofluorescence technique.
The results were expressed as a Mean ± Standard Deviation and the Mann-Whitney-U test was used in statistical analyses.

Results

One of our patients (BU) with selective IgA deficiency was asymptomatic. Six patients, four with selective and two with partial IgA deficiency had allergic diseases (five patients with bronchial asthma and one with food allergy; EÇ, VN, KD, TT, KY, EA). Three patients had hematologic disorders, two with idiopathic thrombocytopenic purpura (FB, GD) and one with autoimmune hemolytic anemia (HA). The other four patients had chronic or recurrent sinopulmonary infections (Table I).
The serum IgA level was 0 in 12 patients, and 16 mg/dl and 22 mg/dl in two patients. The serum IgG levels were high in four patients and the IgM levels were high in two patients (Table I). Total lymphocyte counts were above 2000/mm^3 in all patients.

TABLE I: Clinical Data and Immunglobulin Levels of the Patients

Patients	Sex	Age (Yrs)	Clinical Picture	Serum Ig Levels (mg/dl) IgA	IgM	IgG	Autoantibody
1. UU	M	9	Recurrent infections	0	85	1220	(–)
2. BU	F	34	Asymptomatic	0	148	960	(–)
3. EÇ	M	9	Allergic diseases+ recurrent infections	0	59	700	(–)
4. GC	M	2	Chronic infections	0	77	700	nd
5. VN	M	9	Allergic diseases	0	129	1630	(–)
6. HŞ	M	8	Chronic-recurrent infections	0	138	1240	nd
7. FB	F	6	ITP	0	130	3150	nd
8. AB	F	6	Chronic-recurrent infections	0	319	3490	(–)
9. GD	M	3	ITP	0	89	1560	(–)
10. HA	F	5	Recurrent infections+ hemolytic anemia	226	508	(–)	
11. KD	M	9	Allergic diseases+ chronic infections	0	90	2340	(–)
12. TT	M	10	Allergic disease	0	145	2260	(–)
13. KY	M	7	Allergic disease	16	132	1250	(–)
14. EA	M	5	Allergic disease+ recurrent infections	22	128	710	nd

• Idiopathic thrombocytopenic purpura.

Mean Values of Normal Serum Ig's for the Various Age Groups•

Age Group	IgA (mg/dl)	IgM (mg/dl)	IgG (mg/dl)
2-3	66 ± 16	118 ± 35	889 ± 228
4-6	80 ± 31	130 ± 46	970 ± 186
7-11	130 ± 28	133 ± 39	1191 ± 282

nd : not done

• : The mean values of healthy children (Pediatric Immunology Unit, Hacettepe University Institute of Child Health).

Skin tests in which PHA and *Candida* were applied showed a positive reaction in seven patients. One patient reacted positively to the SK/SD test (Table II).

The percentages of E-rosette forming cells were found to be between 64-78 (mean value 72 ± 4). There was no significant difference observed between the patient and control groups.

In vitro blastogenic response to PHA was found to be low in only one patient (HA). The mean value of the stimulation index which was 40.6 ± 24.8 in the patients, was not significantly different from the controls (Table II).

TABLE II: Cell-Mediated Immunity of Patients

Patients	E-Rosette Forming Cells (%)	In Vitro PHA Response SI	Delayed Hypersensitivity Skin Test PHA	Candida	SK/SD	PPD
1. UU	74	23.2	+	+	–	–
2. BU	73	30.6	nd	nd	nd	nd
3. EÇ	64	53.0	nd	nd	nd	nd
4. GC	70	51.1	+	+	–	–
5. VN	78	nd	nd	nd	nd	nd
6. HŞ	69	31.5	+	+	–	–
7. FB	74	95.4	+	+	–	–
8. AB	78	34.2	+	+	–	–
9. GD	74	22.7	+	+	–	–
10. HA	76	10.6	nd	nd	nd	nd
11. KD	74	57.4	nd	nd	nd	nd
12. TT	71	nd	nd	nd	nd	nd
13. KY	78	29.0	+	+	–	–
14. EA	67	49.6	nd	nd	nd	nd
Patients (n = 14)	72 ± 4	40.6 ± 24.8				
Controls (n = 19)	69 ±6	42.1 ± 17.0				

The mean percentage of B lymphocytes was 18.4 ± 5.8 in eight patients. The percentages of surface Ig bearing cells were as follows: $sIgM^+$ lymphocytes 11 ± 6.2, sIG^+ lymphocytes 7.6 ± 3.5, and $sIgA^+$ lymphocytes 1.8 ± 1.4. There was no significant differences found when comparing the mean values of the patients with those of the controls. Only two patients had no $sIgA^+$ bearing cells (Table III).

The percentages of T lymphocytes (CD^+_3) in 7 patients were between 54-81 and the mean value was 69.4 ± 10.9. The percentages of CD^+_4, CD^+_8 T cells and the CD^+_4/CD^+_8 ratios of the patients were 43.7 ± 11.5, 26.9 ± 6.1 and 1.75 ± 0.88 respectively. The CD^+_4/CD^+_8 ratio was found to be low in two patients. There was no significant difference between the mean values of the patients and the controls (Table III).

Autoantibodies were negative in 10 patients.

TABLE III: Surface Immunoglobulins and T Cell Subpopulations

Patients	B Lymphocytes (Total) sIg+	sIgM+	sIgG+	sIgA+	T Lymphocytes (%) CD^+_3	CD^+_4	CD^+_8	CD^+_4/CD^+_8
1. BU	23	19	7	2	77	49	30	1.63
6. HŞ	13	6	6	3	54	26	24	1.08
7. FB	15	6	7	1	73	38	36	1.05
8. AB	17	10	12	2.5	54	38	29	1.31
9. GD	13	3	5	0	nd	nd	nd	nd
11. KD	15	9	6	0	75	42	23	1.82
12. TT	28	16	14	2	72	62	17	3.64
13. KY	23	19	4	4	81	51	29	1.75
Patients (n = 8)	18.4 ±5.8	11.0 ±6.2	7.6 ±3.5	1.8 ±1.4	69.4 ±10.9	43.7 ±11.5	26.9 ±6.1	1.75 ±0.88
Controls (n = 19)	22.2 ±5.0	8.2 ±4.2	9.1 ±3.6	4.5 ±3.1	66.9 ±13.3	45.6 ±5.2	27.0 ±6.9	1.80 ±0.52

Discussion

Selective IgA deficiency has been postulated to have both autosomal recessive and autosomal dominant forms of inheritance[7,8]. The parents and siblings of seven patients were screened for IgA deficiency, and only one case of selective IgA deficiency was found in these seven families. This patient (BU) was asymptomatic. The absence of IgA in the mother and in one of her children suggests an autosomal mode of inheritance in this family. It has been proposed that a compensatory increase of IgG and IgM in the serum and increased levels of secretory IgM and innate humoral factors may play an important role in obstructing the onset of symptoms in asymptomatic patients[15].

Chronic, recurrent viral or bacterial infections are the most frequent findings in selective IgA deficiency. Recurrent chronic infections were the main complaints in four of our patients. Four other patients who had allergic or hematologic disorders also presented with recurrent and/or chronic infections. The absence of secretory IgA is considered to be the main cause of infection.

Six of our IgA deficient patients had allergic diseases. When compared to the normal population allergic disorders are observed more frequently in individuals with selective IgA deficiency[3,7,8]. Although the cause of the frequent occurrence of allergic diseases is unknown, the absence or deficiency of serum and secretory IgA may lead to impaired neutralization of antigens resulting in a significant increase of IgE synthesis.

Of our three patients with hematologic diseases, two had ITP and one had autoimmune hemolytic anemia. Autoimmune hematologic disorders are seen frequently in selective IgA deficiency but this association cannot be explained by co-existence[16,17].

An increased frequency of autoimmunity in selective IgA deficiency has been observed as in some other primary immunodeficiencies. Amman and Hong[18] found various autoantibodies in ten of 15 patients studied with selective IgA deficiency. In our study, two patients had ITP, and one patient had autoimmune hemolytic anemia. Autoantibodies (anti-nuclear, anti-reticulum, anti-cytoplasmic, anti-parietal cell, anti-smooth muscle, anti-mitochondrial) were found to be negative in the serum of 10 of our patients which corresponds to the findings of the 50 patients evaluated by Burgio et al[3]. The following hypotheses have been proposed to explain the frequent occurrence of autoimmune diseases with selective IgA deficiency[15]: I. Due to the absence of secretory IgA, environmental antigens enter the organism from the mucous membranes. The antibodies produced to react against these antigens may act as autoantibodies because of cross-reactivity. II. The association of autoreactivity with a thymic defect may lead to IgA deficiency. III. Susceptibility to viral infections may stimulate the autoreactivity.

As we observed in some of our patients, the serum IgG and IgM concentrations have been found to be increased in selective IgA deficiency. These increases in the serum IgG and IgM levels occur in compensation for the absence of IgA or originate from associated disease, like chronic infections[19].

The majority of IgA deficient patients have an intrinsic defect in B lymphocytes. Various mechanisms have been assumed in its immunopathogenesis. Of these, an arrest in the development of B cells associated with decreased synthesis or release of IgA rather than the absence of IgA^+ B lymphocytes, or an arrest in the earlier stage of immunoglobulin-producing B cells following normal sequential development of IgM to IgG have been suggested[7,20-24]. In two of our patients, IgA bearing B lymphocytes were not detected. An early intrinsic defect in the maturation of B lymphocytes has been suggested as the cause for the absence of IgA bearing B lymphocytes[20].

However, in some cases, an increase of IgA specific suppressor T lymphocyte activity inhibits the production of IgA by normal B lymphocytes. It has been shown that B lymphocytes in these individuals produce IgA when co-cultured in vitro with normal T lymphocytes[5,6,25,26,27]. In our study the CD^+_4/CD^+_8 ratio was found to be low in two patients which was caused by a decrease of CD^+_4 cells in one patient (HS), and an increase of CD^+_8 in the other (FB). Since quantitative changes of T cell subsets may not always correlate with functional activity, functional studies are needed on this subject.

Although there may be impairment in some cases, cell-mediated immunity is usually normal in selective IgA deficiency[3,23]. In our study, the percentage of E-rosette forming cells was normal in all the patients and delayed hypersensitivity skin tests were positive at least when two antigens were applied to the patients. The evaluation of in vitro lymphoblastic response to PHA showed that the stimulation index was low in only one patient which was probably due to a viral infection that the patient had during the time of the study.

The heterogeneity of clinical and immunological features in these patients suggests that various mechanisms may be responsible for immunopathogenesis of IgA deficiency.

Summary

The clinical and immunological features of 14 patients including 12 with selective and two with partial IgA deficiency are presented. One patient was asymtomatic, six patients had allergic diseases, three patients had hematologic disorders and the remaining patients had chronic-recurrent infections. The IgG and IgM serum concentrations were high in four and two patients, respectively. Delayed hypersensitivity skin tests were applied to seven patients, and were found positive in all. E-rosette forming cells were within the normal range. In vitro lymphoblastic transformation with PHA was normal in all the patients, except for one. Two patients had no $sIgA^+$ B cells. The percentage of CD^+_4 T cells was decreased in one patient and the percentage of CD^+_8 T cells was increased in another, both of whom had a low CD_4/CD_8 ratio. The heterogeneity of clinical and immunological features in these patients suggests that various mechanisms may be responsible for the immunopathogenesis of IgA deficiency.

Acknowledgment

We are grateful to the Departments of Pediatric Allergy, Hematology and Chest Diseases for their help offered in the study of their patients. We also wish to thank Prof. E. Gülmezoğlu for his assistance in the study of autoantibodies.

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The Turkish Journal of Pediatrics 31:209-214, 1989

THE RESISTANCE OF ABSORBABLE SUTURES IN FETAL TISSUE AND FLUIDS*

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Key words: sutures, fetal surgery

Despite the widespread clinical and experimental applications of intrauterine (IU) surgery, we could not find, after a thorough search of the literature, any studies published which describe the resistance of sutures under IU conditions. However, Adzick and co-workers[1] have demonstrated that the uterine closure with nonabsorbable material results in a decrease in fertility in animals. How fetal tissue, and especially amniotic fluid, which exhibit changes in composition during the last ten weeks of pregnancy[2,3] affect sutures, remains unknown. This study was designed to investigate the resistance of three different types of absorbable sutures under IU conditions, which are extensively used in "extra-uterine" surgery.

Material and Methods

Fifteen centimeter lengths of 4/0 chromic catgut (CC), proglactin 910 (V) and polydioxanone (P) suture materials were incubated in three groups:

Group I: By opening wide the amniotic sac of a ten-day-old chicken embryo (CE) of the genus *Gallus domestica*, amnioallantoic fluid and space formed using the technique described in previous reports[4-7]. One suture was incubated in each of these amnioallantoic cavities.

Group II: Using the same technique, one of the lower extremities of the CE was sutured, and the remainder of the suture was placed in the amnioallantoic cavity. All the eggs with CE and sutures were incubated at 38°C and in 90% humidity until the sutures were removed for measurement.

Group III: Human amniotic fluid collected during elective cesarean section operations in the thirty-eighth week, which had no known infection, was used for in vitro incubation at 37°C. A piece of each suture was incubated in a separate bottle.

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If the CE was infected or dead, or if the human amniotic fluid had become infected, the experiment was repeated for those specimens. Fifteen suture samples were tested at the beginning of the study in order to determine their initial tensile strengths. At the end of the study, ten samples of each suture were tested for two, four, six, eight and ten day periods in groups I and II, and for two, four, six, eight and ten week periods in group III. After washing the sutures in sterile saline, the tensile strengths were calculated using a Statimat II tensiometer operating at a speed of 50 mm/min. Tensile strengths were calculated as a percentage of the initial mean tensile strength of each type of suture. Student's *t* test was used to make a statistical evaluation of the results.

Results

The initial tensile strengths of CC, V and P sutures were (Mean ± SD) 1070 ± 126, 1912 ± 46, and 1923 ± 55 grams, respectively. The resistance curves of the sutures in amnioallantoic fluid are shown in Fig. 1, and in fetal tissue in Fig. 2. On the tenth day of the experiment, the preserved resistance of CC, V and P in chicken amnioallantoic fluid was 68 ± 6.0, 78 ± 5.0 and 80 ± 7.5 percent, respectively. For the first six days the resistances of the sutures did not significantly differ from each other. On the eighth and tenth days, CC had a

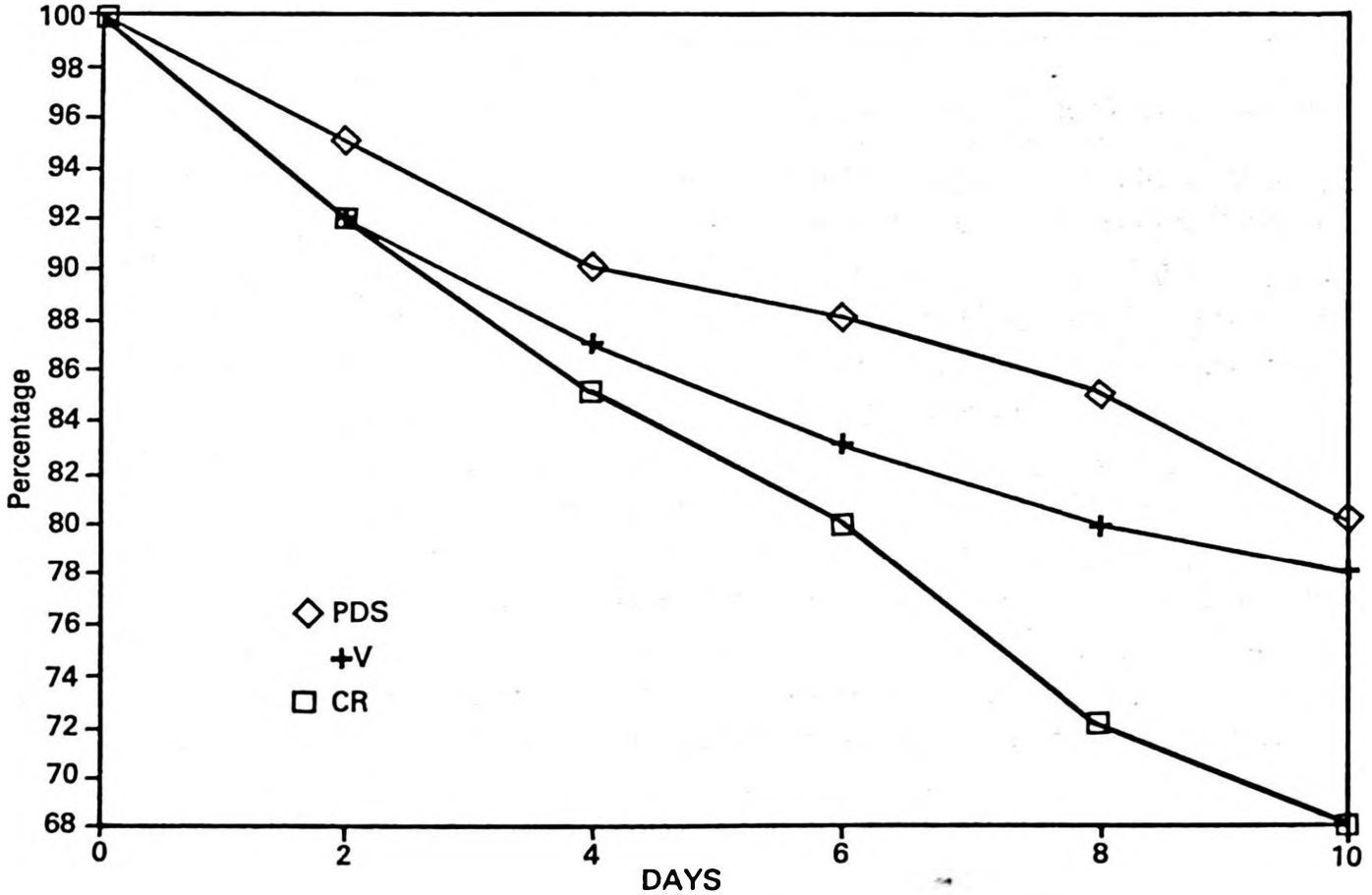

Fig. 1: Resistance curves of sutures in amnioallantic fluid of chicken embryo expressed as a percentage of initial tensile strength

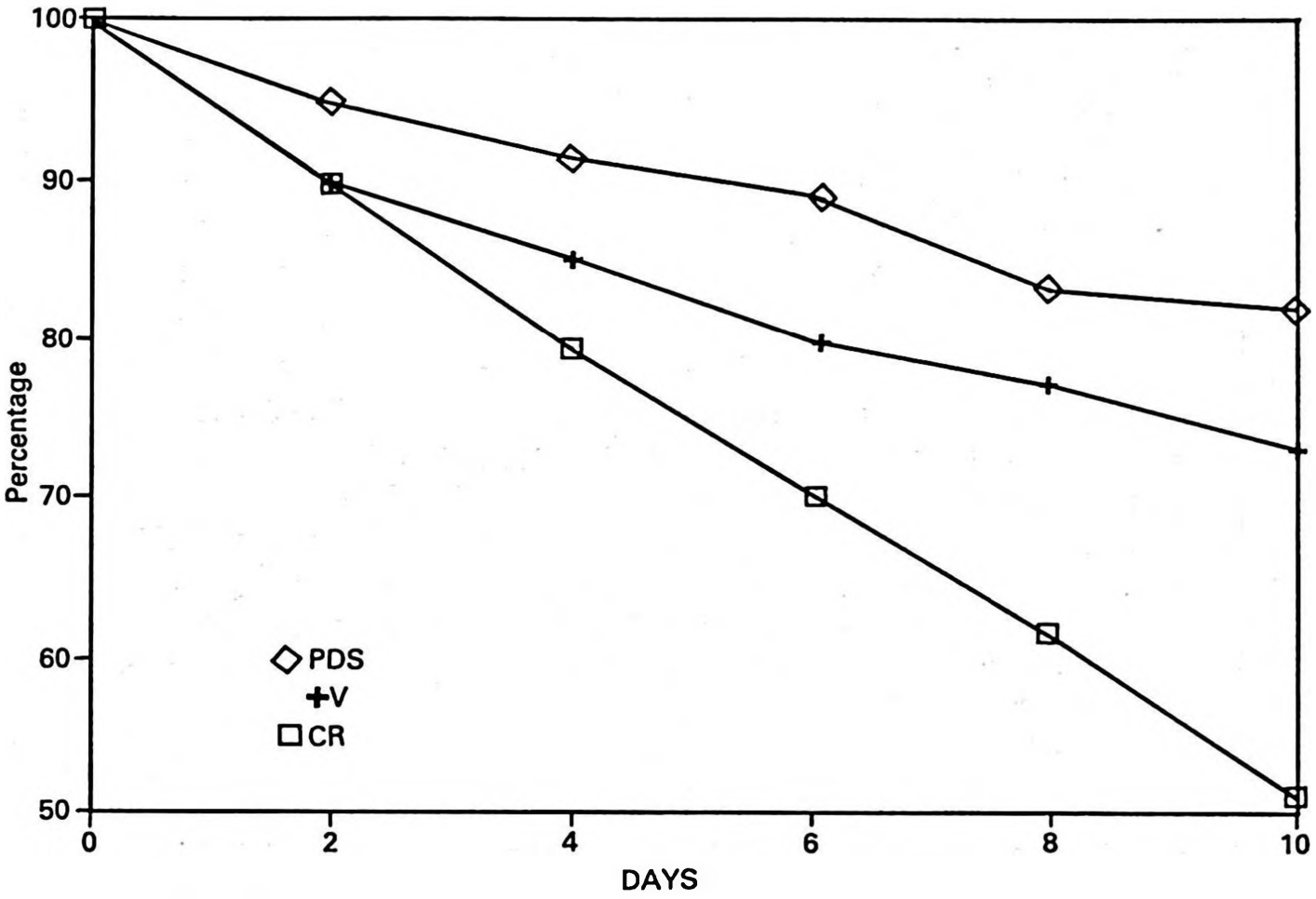

Fig. 2: Resistance curves of sutures in fetal tissue of chicken embryo expressed as a percentage of initial tensile strength.

statistically impaired loss of tensile strength when compared to the other types ($p < 0.01$). On the tenth day, the preserved resistance of CC, V and P in chicken fetal tissue was 51 ± 6.9, 73 ± 5.7 and 82 ± 6.7 percent, respectively. CC also had a significant loss of resistance in fetal tissue after the fourth day when compared to V and P ($p < 0.01$). V had a greater loss in tensile strength than P in fetal tissue on days two, six, and ten ($p < 0.01$).

When differences in resistance between incubations in fetal fluid and tissue were investigated no distinction was found for V and P. But CC could not preserve its resistance in fetal tissue, as it had done in the fluid. The difference was 17 percent on the tenth day and significant after the second day ($p < 0.05$ on the second day and $p < 0.01$, thereafter).

Resistance curves following in vitro incubation with human amniotic fluid are shown in Fig. 3. In the tenth week, the retaining resistances of CC, V and P were 10 ± 5.8, 35 ± 7.5 and 47 ± 12.2 percent, respectively. P preserved its tensile strength better than the other two sutures ($p < 0.01$ for the last eight weeks) and V preserved its resistance better than CC for the last four weeks ($p < 0.01$).

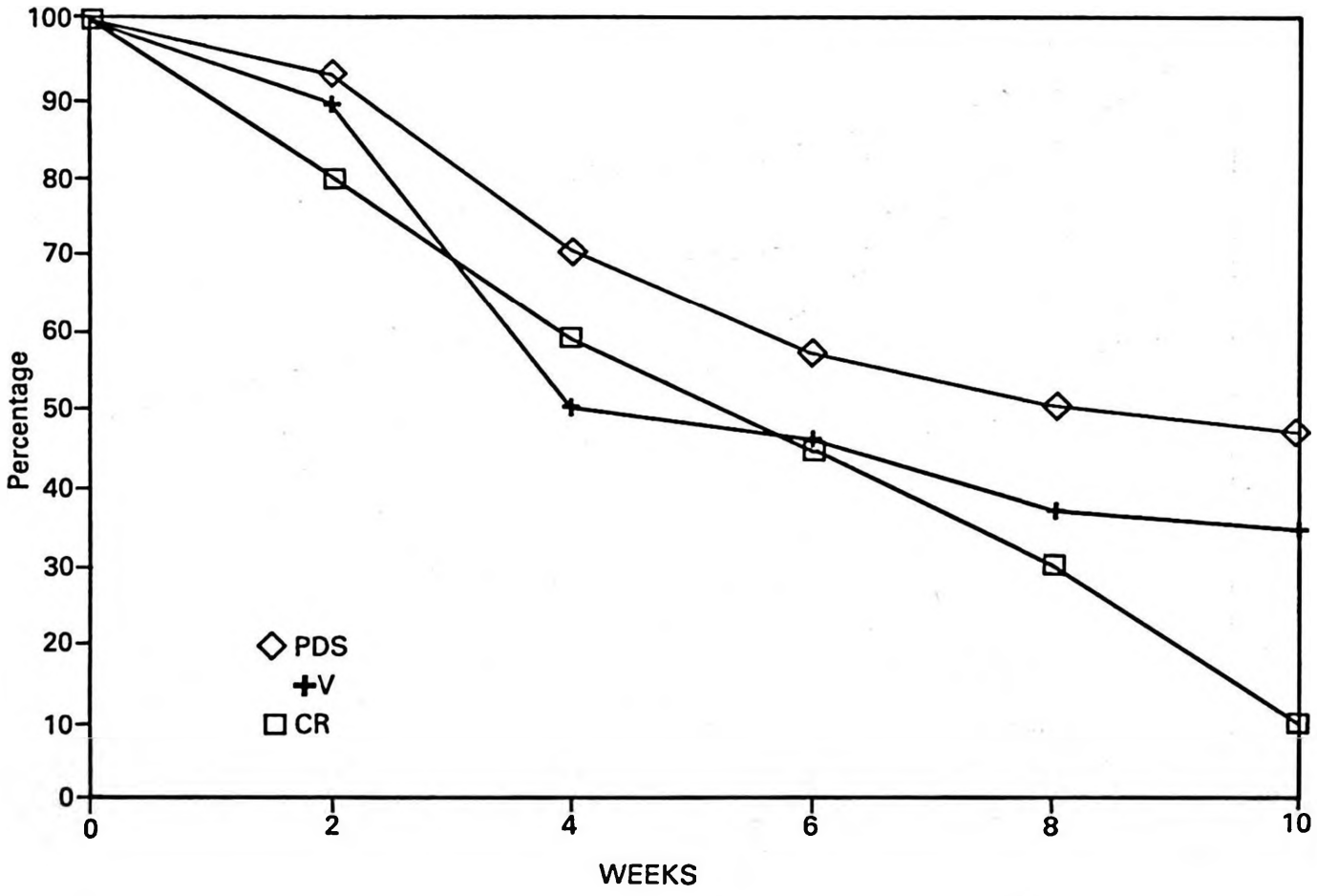

Fig. 3: Resistance curves of sutures after in vitro incubation with human amniotic fluid expressed as a percentage of initial tensile strength.

Discussion

The resistance of absorbable sutures is affected by environmental conditions. Chromic catgut in the human stomach is destroyed within 24 hours[8], and polyglycolic acid in proteus infected urine within three days[9]. Data regarding the effect of fetal tissue and fluids on the resistance of sutures would be a reference for the selection in IU surgical practice.

In the present study, we demonstrated that the resistance of V and P in fetal tissue was approximately the same as that in fetal fluids. On the other hand, the resistance of Chromic catgut disappeared more rapidly in fetal tissue than in fetal fluid. The reason for this difference may be the presence of different absorption mechanisms in sutures. Chromic catgut is absorbed by proteolysis, and the other two types of sutures by hydrolysis[3]. As a result of a slow loss of resistance in fetal fluids, the particles of CC dermal sutures in fetuses would transmit into free foreign bodies in amniotic fluid after some time of IU surgery. This is not the case for the other two types of sutures.

Human amniotic fluid has a lower osmolarity and sodium level and a higher urinary excretion of substances than the other body fluids during the last ten weeks of

pregnancy[2,3]. However, this did not affect the resistance of the sutures in this study. All three suture types preserved some of their tensile strengths until the tenth week, practically the same as they had been preserved in tissue[8]. Since it was not possible for us to carry out this study in collaboration with the gynecology department of our University where routine amniosyntesis is performed, we were not able to determine the effects of amniotic fluid prior to the thirty-eighth week of pregnancy.

Since the physiologic osmolarity of body fluids in birds is nearly 1.5 times lower than that in mammals[6], the CE model may be not a plausible one. However, the cost of this model is quite low, and it can be easily implemented in a hospital without a research laboratory. Therefore, we preferred this model for our study. Due to certain technical problems, studies on fetal tissue reactions to sutures and the effects of sutures on IU growth could not be performed. Further investigations into such studies might result in a more liberal use of suture materials in IU surgery.

Summary

The resistance of three different types of absorbable suture materials was studied in three groups which simulated intrauterine conditions. In group I the sutures were incubated in the amnioallantoic cavity of chicken embryo (CE) and in group II in the fetal tissue of CE. For incubation of sutures in group III, human anmiotic fluid collected during cesarean section operations in the thirty-eighth week of pregnancy was used. We discovered that chromic catgut had a lower resistance in fetal tissue than in fetal fluid ($p < 0.01$), which could be an important point in the selection of fetal dermal sutures. In vitro incubation in human amniotic fluid did not effect the known rate of loss of chromic catgut, proglactin 910 and polydioxanone.

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The Turkish Journal of Pediatrics 31:215 - 220, 1989

TREATMENT OF NOCTURNAL ENURESIS: A PLACEBO-CONTROLLED TRIAL WITH PIRACETAM, DIPHENYLHYDANTOIN AND PSYCHOTHERAPY*

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Key words: diphenylhydantoin, enuresis, piracetam, psychotherapy

Various types of medication and methods have been used in the management of nocturnal enuresis (NE), even though this condition mostly subsides spontaneously with age[1-3]. Considerable controversy has arisen regarding the therapeutic effectiveness of piracetam[4,5]. This placebo-controlled study was undertaken in a bid to settle the conflict regarding the use of piracetam in the treatment of NE.

Material and Methods

Of 730 outpatients (374 males and 356 females) aged between 6-14 years who were questioned at the Ankara S.S.K. Children's Hospital for NE, 201 children (117 males and 84 females) were found to be enuretic.

One-hundred enuretic children were randomly selected whose history, physical examination, urinalysis and urine culture were negative for diurnal enuresis, encopresis, urinary tract infection and organic defects. There were 27 patients who had been excluded from the study because they either were not cooperative or failed to come for their visits to the hospital. Electroencephalograms (EEG) of all the patients and 20 of the non-enuretic children (controls) were blindly evaluated. The intelligence quotient (IQ) of 56 enuretic and 16 non-enuretic children, who had been randomly selected were determined by using Wechsler's Intelligence Scaling Score (WISC). Also the IQs of 21 patients receiving piracetam were measured at the end of the eighth week of the study.

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The patients were randomly assigned into four of the following treatment groups: Group I consisted of 18 patients who had received piracetam (Nootropil^{R}) in a single dose of 20 mg/kg (maximum 800 mg) at bedtime. Group II consisted of 15 patients who had received play or supportive therapy[6,7] for ten weeks in weekly sessions, each session lasting for at least 40 minutes. Group III (combined treatment group) consisted of 12 patients who had received both drug and psychotherapy for eight weeks. Group IV consisted of 14 patients who had received a single dose placebo at bedtime. Group V consisted of 14 patients who had received diphenylhydantoin (Epdantoin^{R}) in a dose of 5 mg/kg/day. Although the epileptic patients were not considered to be enuretic, the EEGs of the 14 enuretic children in Group V revealed epileptic abnormalities.

All patients were seen at the end of the second, sixth and eighth weeks. Therapeutic effectiveness was graded as follows: 0-no improvement, 1-partial improvement, 2-complete cure. The classical Chi square, Fisher's exact test and variance analysis were used to evaluate the differences.

Results

Of seven hundred and thirty children aged between six and 14 years (mean: 9.2 ± 2.17) who were questioned, 201 (27.5%) children (male/female ratio: 58/42; mean age: 8.5 ± 2.3 and 8.4 ± 1.9, respectively) were found to be enuretic. Of these, 31 percent were males and 24 percent were females, and 10.1 percent were between 6-7 years of age and 3 percent were over 11 years of age.

EEG abnormalities, e.g. random spike discharges, diffuse high voltage slow waves and "build-up" phenomenon, were found more frequently in the enuretics (29% of the enuretics and none of the controls). The IQs of the enuretics were found to be significantly lower ($p < 0.05$) than those of the non-enuretics (compared with controls it was 94.68 ± 2.43 and 104.25 ± 2.83, respectively). The EEGs and IQs of all treatment groups (excluding the EEGs of Group V) showed no statistically significant ($p > 0.05$) differences. The IQs did not significantly affect the therapeutic responses ($F = 0.139$; $p > 0.05$). No significant differences in the IQs of Group I were observed after treatment.

Therapeutic response is summarized in Table I. A complete cure observed in Group III was significantly ($X^2 = 10.86087$; $p < 0.05$) higher than the other groups. If we consider partial improvement a positive response, then both psychotherapy and combined therapy (Groups II and III) can be said to have a significant effect ($X^2 = 1.376633$, $p < 0.05$). There were no significant differences between Groups I, IV and V. No side-effects were observed except for mild headache and nausea during the course of treatment with piracetam.

TABLE I: Summary of Therapeutic Responses in the Treatment of Nocturnal Enuresis

Group	Drug and Method	Response+ 0 n	0 %	1 n	1 %	2 n	2 %	Total
I	Piracetam	9	50	7	39	2	11	18
II	Psychotherapy	–	–	8	53	7	47	15
III	Combined group	–	–	4	33	8	67++	12
IV	Placebo	4	28	5	36	5	36	14
V	Diphenylhydantoin	4	28	6	44	4	28++	14

+See text, ++X^2= 10.86087, $p < 0.05$

Discussion

NE is defined as involuntary "bedwetting" if it occurs at least twice a month after an age (mostly five years) when bladder control is expected to have been attained[8]. Although there is no general agreement concerning the age at which enuresis should be considered abnormal[9], some authors propose that children should not be labelled enuretic unless wetting persists at least once a week past the age of five years in girls, and from six to ten years of age in boys[3].

It has been established that the presence of stress factors occurring during the developmental period, that is, between the ages of two to four[10], a time at which bladder control has not yet been fully acquired, may cause NE which may be improperly diagnosed as "primary" NE. Therefore, it is difficult to classify enuresis as primary or secondary simply by evaluating a period of six or twelve months of "dry nights"[3]. For this reason we did not divide our patients into groups of primary and secondary enuresis.

Jarvelin et al[11] found that the incidence of enuresis among low birth-weight children was greater than among normal birth-weight children, and that children with both diurnal and nocturnal enuresis were found to have the lowest birth-weights among enuretics. They assumed that the reason for this may be that neurological damage is most obvious in low birth-weight children. Jarvelin et al[11] referred in his study to Shaffer et al[12], who suggest that enuresis can be classified into two groups: those with and those without associated neurodevelopmental abnormality. They assumed that neurologically damaged children experience both diurnal and nocturnal wetting while children with delayed maturation experience mainly night-wetting with genetic predisposition. Inoue et al[13] reported that the rhythmic slow wave observed in nocturnal sleep encephlograms in children with

NE may also be caused by the immaturity of the sleep mechanism in enuretic children. Some authors[14,15] have suggested that epilepsy plays a role in the etiology of enuresis, while others[16,17] do not accept it as being a nocturnal manifestation of classical convulsive epilepsy. Kaada and Retvedt[18] assumed that epilepsy and primary NE may be the effect of the same higher level brain dysfunction or of cortical instability resulting from delayed maturation. Our results failed to show any beneficial therapeutic effectiveness of antiepileptic treatment with diphenylhydantion in NE after a period of 8-10 weeks.

Several drugs and methods have been suggested in the management of NE which have had varying rates of success. Chemotherapy using imipramine and desamino-D-arginine-vasopressin and "alarm and conditioning" therapy have been found to be most effective[3,4,8,19-26]. Piracetam, a nootropic agent, is claimed to improve alertness thereby speeding up mental performance, acts on the cortical control of subcortical brain structures, has a certain protective effect against the consequences of induced brain hypoxia, and has an enuretic activating effect on the cortex[5,27]. Pogady et al[5], who treated 37 children with piracetam, reported a rate of improvement of more than 50% in 81% of the patients, while Yurdakok et al[4] reported no significant therapeutic effects after six weeks treatment with piracetam.

In the present study piracetam (Nootropil^{R}) was administered to 30 patients (12 patients were given the drug in combination with psychotherapy), and we found that the therapeutic effects did not differ from those given the placebo.

In our patients a complete cure rate of 67% and a partial improvement rate of 33% were achieved with play and/or supportive therapy combined with piracetam (the same as the placebo group).

We recommend play and/or supportive therapy in association with a placebo as the first step in the management of NE which is in agreement with Novello[3] and also other researchers[28], who suggest that medication should never be prescribed in isolation in treating this condition.

Summary

The study population consisted of 100 children with nocturnal enuresis (NE) aged between six and 14 years, who had been randomly selected amongst the enuretic outpatients at the Ankara S.S.K. Children's Hospital. A placebo-controlled evaluation of piracetam, diphenylhydantoin and psychotherapy was carried out. At the end of the eighth week of the study, it was discovered that the therapeutic effects observed in the patients administered piracetam did not differ from those given the placebo. Therefore, we recommend that psychotherapy in association with a placebo be the first step in the treatment of NE children.

Acknowledgment

We wish to thank Dr. Osman Saka, Department of Biostatistics, Hacettepe University, Ankara, for his statistical evaluations and analyses.

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The Turkish Journal of Pediatrics 31:221 - 225, 1989

EFFECT OF D-PENICILLAMINE ON THE FETAL LUNG OF RATS: A MODEL FOR CONGENITAL EMPHYSEMA*

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Key words: D-penicillamine, copper, lung, congenital emphysema, rat

The pathogenesis of pulmonary emphysema is characterized by permanent abnormal enlargement of the distal air spaces due to destruction of their walls, the etiology of which is yet unclear. Since the structural and elastic properties of the lung depend primarily on the connective tissues, collagen and elastin, they may play an important role in the pathogenesis of emphysema[1].

Copper is an essential component of lysyl oxidase which is important in the cross-linking of collagen and elastin. It has been demonstrated that the cross-linking of collagen and elastin in mice is impaired by penicillamine, and that the lung structure and function of these mice also reveal abnormalities[2,3]. The aim of this study is to evaluate the effects of penicillamine on the development of lung tissue in the fetal rat.

Material and Methods

Pregnant albino rats, with a mean weight of 250 g (range between 220 to 300 g) were used in this study. Their gestational ages were determined by the presence of a vaginal plug on the first day of gestation, and abdominal palpation after the tenth day.

Six animals received a daily dose of either 300 mg (low-dose) or 400 mg (high-dose) of D-penicillamine (DPA) in their drinking water during their last six days of gestation. Two rats were used as controls and received no drug. Between the twentieth to twenty-first days of gestation the fetuses in the four animals of the study group (two high-dose and two low-dose) and in one of the controls were delivered by cesarean section. The remaining two animals, who received low-dose DPA during their gestation, and one control, were given a normal diet containing no DPA for three weeks after delivery, which included the lactation

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period. At the end of this period their offspring were sacrified and evaluated in the same manner as the newborn animals. The serum copper levels were determined in all the animals, and it was demonstrated that these levels had decreased in the study group (83 and 87 mg/dl in low-dose; 69 and 71 mg/dl in high-dose) more than in the control group (95 and 98 mg/dl). However, the serum copper levels were the same both in the study group and the control group three weeks after delivery (92.93 and 95 mg/dl).

The offspring were weighed and then killed by decapitation. Their lungs were removed, weighed, embedded in paraffin blocks, stained with hemotoxylin-eosin and examined using light microscopy.

All the tissues were evaluated for the presence of bronchomegaly, cystic alveoli, atelectasis, vascular aneurism, perivascular loose connective tissue and pulmonary hemorrhages. The findings were evaluated statistically according to Student's *t* test.

Results

It was observed that D-penicillamine treatment during gestation caused marked growth retardation in the offspring. Although the lung weight to body weight ratio in the newborn animals did not differ between the low-dose and control groups, it was significantly decreased in the high-dose group (Table I).

TABLE I: Effect of D-Penicillamine on Lung Tissue (Macroscopic Findings)

	DPA During Gestation	Body Weight (gm)	Lung Weight (gm)	LW / BW × 100
At the end of gestation	1. None (n:7)	9537 ± 390	258 ± 64	2.69 ± 0.57
	2. Low-dose (n: 10)	8378 ± 483	233 ± 56	2.78 ± 0.63
	3. High-dose (n: 8)	4897 ± 579	94 ± 15	1.92 ± 0.29
In the third week	4. None (n: 8)	15083 ± 1482	356 ± 53	2.43 ± 0.48
	5. Low-dose (n: 6)	13034 ± 1614	226 ± 42	1.75 ± 0.34
	Statistical comparisons			
	1-2	$p < 0.001$	$p > 0.05$	$p > 0.05$
	1-3	$p < 0.001$	$p < 0.001$	$p < 0.01$
	2-3	$p < 0.001$	$p < 0.001$	$p < 0.005$
	4-5	$p < 0.05$	$p < 0.001$	$p < 0.01$

LW : Lung weight

BW. Body weight

The hematoxylin-eosin stained histologic sections of the lungs in the study group showed bronchomegaly, cystic alveoli, atelectasis, vascular aneurism, perivascular loose connective tissue, and small hemorrhagic foci. Resumption of a normal diet in the animals of the study group for a period of three weeks did not restore the lung tissue to normal (Table II; Figs. 1, 2).

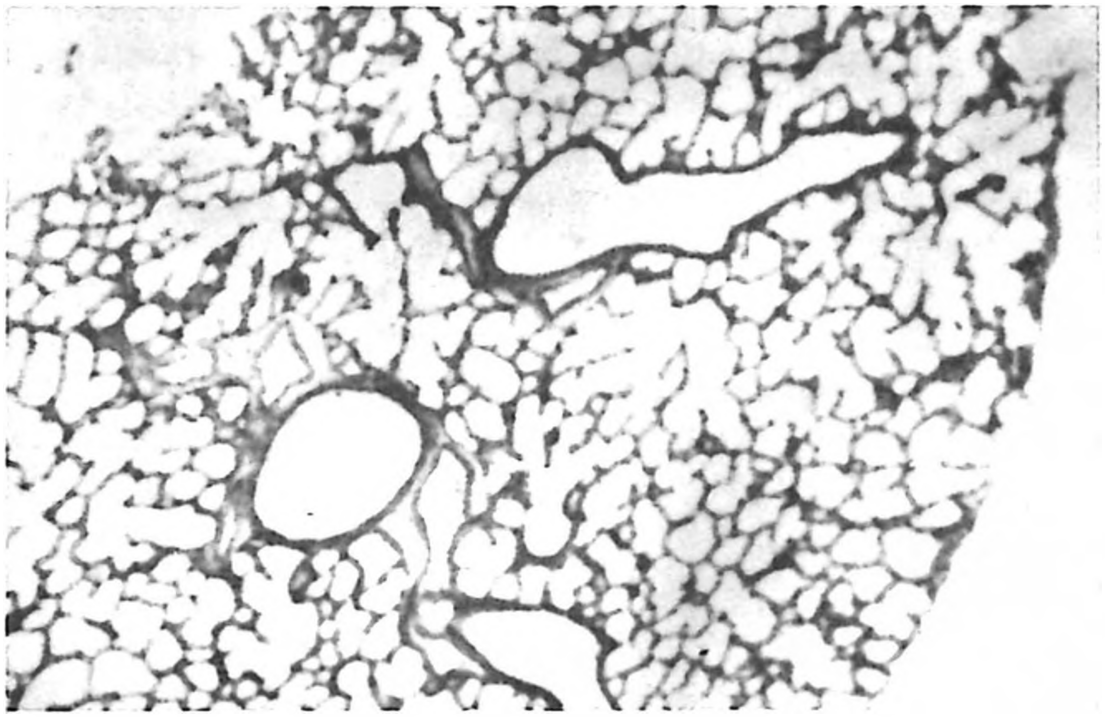

Fig. 1: Bronchomegaly, large irregular alveolar ducts and alveoli in DPA treated animals.

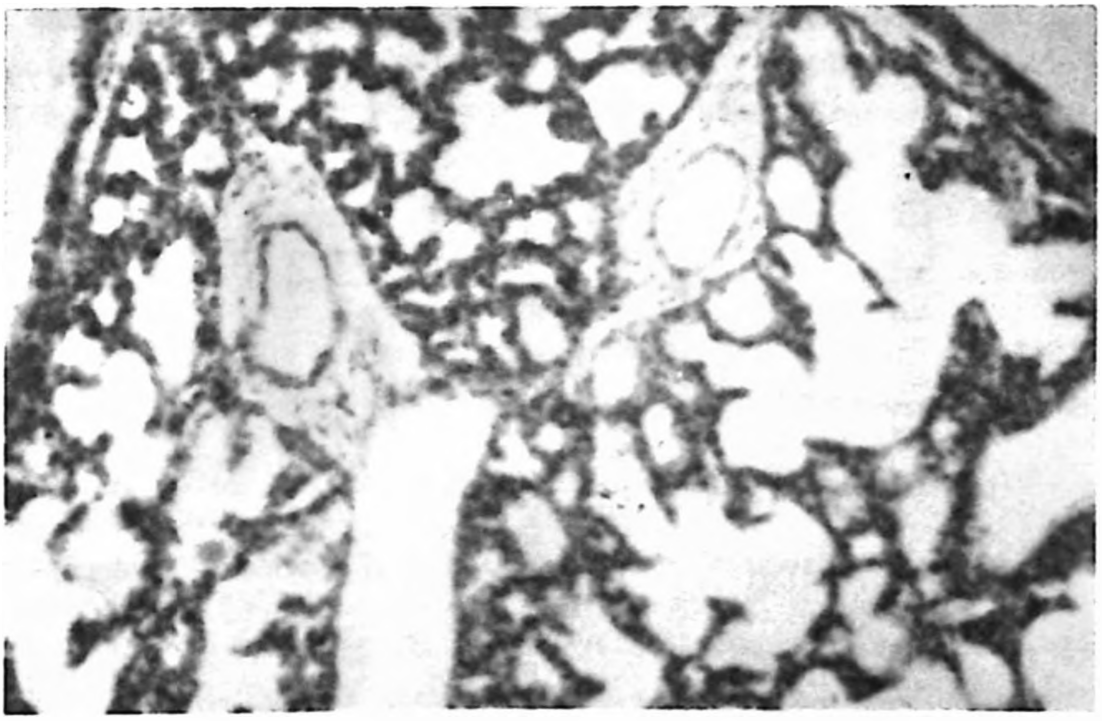

Fig. 2: Perivascular loose connective tissue in the lung.

TABLE II: Effect of D-Penicillamine on Lung Tissue (Microscopic Findings)

	DPA During Gestation	Bronchomegaly	Cystic Alveoli	Atelectasis	Vascular Aneurism	Perivascular Loose Connective Tissue	Hemorrhage
At the end of gestation	1. None (n: 7)	0%	0%	0%	0%	0%	0%
	2. Low-dose (n: 10)	40%	40%	40%	20%	35%	50%
	3. High-dose (n: 8)	80%	60%	50%	85%	90%	80%
In the third week of gestation	4. None (n: 8)	0%	0%	0%	0%	0%	0%
	5. Low-dose (n: 6)	20%	40%	20%	20%	20%	30%
Statistical comparisons							
	1-2	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.005$
	1-3	$p < 0.001$	$p < 0.001$	$p < 0.005$	$p < 0.001$	$p < 0.001$	$p < 0.001$
	2-3	$p < 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.005$	$p < 0.005$	$p < 0.05$
	4-5	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

Discussion

This study demonstrates that copper-deficient rats born of dams fed with DPA added to their diet during gestation had enlarged alveolar ducts and alveoli. Resumption of a normal diet, free of DPA, fed to the animals during the first three weeks of life did not restore the alveolar structure to normal.

Copper is an essential component of lysyl oxidase, the enzyme which catalyses the oxidative deamination of lysine residues in the precursor proteins of elastin and collagen[4]. Lysyl oxidase plays a key role in the cross-linking of collagen and elastin[4]. Thus, one would expect a deficiency of copper to result in a metabolic defect such as a decrease of elastin or collagen concentration. The main pathological feature in the lung tissues of the fetal rats was an alteration in the structure of the alveoli which we observed, and which has been reported by other investigators. The cause of this abnormality might result from lysyl oxidase deficiency[2-5]. Since the addition of copper appeared to restore the structure of parenchymal elastin, but did not reverse the structural abnormality of the lung, one must conclude that copper exerts a critical metabolic function in the development of the lung.

Summary

D-Penicillamine administered orally in daily doses of 300 mg or 400 mg to pregnant rats during the last six days of gestation caused marked growth retardation, a decrease in the lung weight to body weight ratio and histological features characteristic of pulmonary emphysema in the newborn animals studied. It was also demonstrated that a normal diet given to the dams for a period of three weeks after delivery did not restore the lung tissue of the offspring to normal.

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The Turkish Journal of Pediatrics 31:227-231, 1989

POST-IRRADIATION OSTEOSARCOMA OF THE ILIAC BONE: A CASE REPORT*

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Key words: osteosarcoma, secondary tumors, radiation complications, rhabdomyosarcoma

The carcinogenic effect of ionizing radiation was recognized as early as a decade of its discovery[1-3]. Leukemia, lung cancer, thyroid cancer, and sarcomas of the bone and soft tissues are well documented examples of radiation-induced malignancies[4,5,6]. Following the advances made in the field of oncology, the incidence of secondary cancer has been rising parallel to the increase in the number of long-term survivors who received therapeutic irradiation[3,5,7]. It is reported that nearly 10-12 percent of long-term survivors may develop a second neoplasm, benign or malignant, within 30 years of the initial therapy[2,8,9].

One of the earliest recognized secondary malignancies to develop following radiotherapy given in the management of various disorders was sarcoma of bone; and such a case was first reported in 1922[6,10,11]. Since then, more than 250 cases of post-radiation sarcoma of bone have been reported[3]. Its incidence is reported to vary between 0.03% - 0.2%. These figures, though not very high, are considerably higher than the natural incidence of primary occurring sarcoma of bone which is estimated at five cases in every 100,000[4]. In a comprehensive study on the incidence of second primary tumors among childhood cancer survivors conducted by Hawkins et al[12], it was found that the relative risk of secondary malignant bone tumors associated with radiotherapy was about twenty-fold the expected number, and that they occurred mostly in the form of osteosarcoma. These serious sequelae gain further importance in pediatric age-group patients who are likely to live long after successful radiotherapy, chemotherapy or both.

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The following case of osteosarcoma of the right iliac bone in a child developing 12 years following the irradiation of an extensive retroperitoneal rhabdomyosarcoma is noteworthy because it developed in a long-term survivor of such a primary tumor. The tumor was confirmed both histologically and radiologically.

Case Report

A five-year-old girl was admitted to Hacettepe University Children's Hospital on January 6, 1975, with the complaint of abdominal pain of two months' duration. It was learned from her family that she had been operated on one month before for an abdominal mass detected on physical examination, without definite diagnosis.

Physical examination on admission revealed a slightly pale child who was in fair general condition. Her temperature was 36.5°C, pulse rate 124/min, and blood pressure reading 110/60 mmHg. The abdominal circumference measured 53 cm. She weighed 16 kg and her height was 103 cm. On abdominal palpation a mass of 29 × 15 cm was found on the right side of the abdomen which extended down to the pelvis. No other pathological findings were detected. Laboratory studies revealed a hemoglobin of 11.4 g/dl, white blood cell count of 6400/mm, normal differential count and urine examinations. Chest X-ray was normal. The IVP revealed a non-functioning right kidney with lateral displacement of the left ureter and indentation of the mass on the bladder. On January 7, 1975, the patient was operated on, and a hard, immobile mass was discovered in the right side of the abdominal cavity, almost occupying the entire abdomen, and fixed to the peritoneum, bowels and omentum. Only a biopsy could be taken, the microscopic examination of which revealed the diagnosis of embryonal rhabdomyosarcoma. According to these findings the patient was classified retrospectively as being in Stage III of the disease (Intergroup Rhabdomyosarcoma Study)[13]. A combined chemotherapy regimen of VAC (vincristine-i.v. actinomycin-D i.v. cyclophosphamide-p.o.)[14] was initiated post-operatively which was continued during and after radiotherapy. From January 16, 1975 to February 25, 1975, a total dose of 4500 cGy in 23 fractions was delivered to the tumour through adequate abdomino-pelvic anterior and posterior parallel opposed fields. The left kidney and the liver were protected in tolerance levels. By the termination of radiotherapy the mass reduced to 4 × 4 cm in size.

The patient did well in her follow-ups and continued chemotherapy regularly for a period of 22 months, till October 1976. Whereafter, she developed bouts of intermittent hematuria which after the necessary investigations was initially interpreted as benign recurrent hematuria. The cystoscopy performed in March 1981, revealed the diagnosis of hemorrhagic cystitis, probably related to cyclophosphamide. In August 1987, she returned to the hospital complaining of a recent painful swelling in the right hip following a traumatic event. On physical examination

there was a tender mass measuring 10 × 15 cm covering the right hip and extending into the pelvis. The roentgenograms of the pelvis showed an increased density of the right iliac bone with new bone formation extending to the adjacent soft tissues, and a "sun burst"-type periosteal reaction, suggesting osteosarcoma. The bone radionuclide scan revealed hyperactivity on the right innominate bone. Laboratory tests showed an elevated level of serum alkaline phosphatase of 232 IU. An open biopsy was taken from both the iliac bone and soft tissue which revealed the diagnosis of osteosarcoma. The patient was initiated on the T-10 chemotherapy protocol adopted by the Memorial Sloan-Kettering Cancer Center, starting with a high dose of 10 gm/m^2 of methotrexate[15]. Though surgical treatment was planned for the patient, this intervention was abandoned upon the detection of multiple pulmonary metastases in the thoracal CATs performed following the administration of six doses of methotrexate therapy. The treatment was continued with maintanance chemotherapy of the same regimen (cisplatin, adriamycin, bleomycin, cyclophosphamide, actinomycin D). An assessment made at the end of two courses showed no evidence of response in the metastatic disease, though there was a mild regression on the primary site.

In June 1988, the patient suffered a severe bout of hematuria which could not be controlled by conventional methods, and subsequently, a cystectomy was performed. The patient died on July 21, 1988, as a result of renal failure and septicemia besides advanced malignancy.

Discussion

Radiotherapy appears to be involved in the formation of many second primary tumors in childhood particularly after being used in treatment of retinoblastoma, central nervous system tumors, Wilms' tumor and Hodgkin's disease[2,5,8,12]. Secondary tumors following irradiation of soft tissue sarcomas are less frequent and sporadically reported[2,5,6,8,9,16]. Among the reported cases, the occurrence of osteosarcomas is even less. And as far as we could review the literature, we were able to detect only few cases of osteosarcoma following therapeutic irradiation for rhabdomyosarcoma[5,6,10,11]. This low incidence may be attributed to the relatively small number of long-term survivors among rhabdomyosarcoma patients for the present time.

The literature reports a wide range of radiation doses (1500-8500 cGy) which is complicated by osteosarcoma[5,8,12,16,17]. In the series reported by the Memorial Sloan-Kettering Cancer Center and the Mayo Clinic which comprises half the cumulative cases, the doses are above 2000 cGy[11].

The criteria for the diagnosis of post-irradiation osteosarcoma were established by Cahan et al in 1948[1]. They proposed that there should be no histologic or radiologic evidence of bone malignancy before irradiation, the secondary sarcoma

must arise within the radiotherapy field, there should be a latent period of a minimum of five years between radiotherapy and the clinical presentation of secondary sarcoma, and finally there must be histologic proof of the malignant tumor. Our case of osteosarcoma of the right iliac bone developing 12 years after therapeutic radiation for rhabdomyosarcoma with normal underlying bone, fulfills all the above-mentioned criteria.

Radiation-induced sarcomas of bone generally have a poor prognosis and the prognosis for sarcomas developing in the axial skeleton which are less commonly effected than long bones, is even worse[3]. In a series of 78 cases of post-irradiation osteosarcoma from the Mayo Clinic it was found that 30 percent of the patients with sarcomas of the extremities lived past the five-year survival rate without recurrence of disease, while none of the patients with sarcomas of the vertebra, pelvis and shoulder girdle did[10]. This difference in prognosis may be explained by the difficulty encountered in applying surgery, which is the primary treatment for osteosarcoma in these localizations. Our patient died of advanced local and metastatic disease only a few months after diagnosis. Our case coincides in this respect to similar cases reported in the literature[3,10]. The question remains as to whether or not the administered VAC combined chemotherapy played a role in the induction of osteosarcoma; as to our knowledge up until now no study has been reported to date regarding this.

It is worth mentioning here that the diagnosis of this rare but serious complication of radiotherapy should not outweigh its benefit in the management of cancer. It is of importance to keep this and other adverse effects in mind while planning radiotherapy, particularly in children with malignancies of long-term disease free expectation. It is also advantageous to remember that with recent advances made in the field of oncology, the relative incidence of treatment-related secondary malignancies will keep rising with life prolongation, therefore, a life-long follow-up seems to be necessary in children treated and cured of their primary cancer.

Summary

A case of osteosarcoma of the iliac bone developing 12 years after the successful management of childhood rhabdomyosarcoma is presented. The frequency of secondary tumors, mainly bone malignancies, following therapeutic irradiation in the pediatric age-group, and the criteria for the diagnosis of radiation-induced bone sarcoma are discussed.

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The Turkish Journal of Pediatrics 31:233-237, 1989

EPIDERMOID CYST OF THE SPLEEN*

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Key words: epidermoid cyst, splenic cyst, spleen

Non-parasitic, benign cysts of the spleen are exceedingly rare. A simplified and current classification of these cysts was published in 1958[1-3]. Of over 650 cases of benign cysts reported in the world literature[4], epidermoid cysts comprise approximately ten percent[1,2,5]. They occur predominantly in children (generally under the age of 15) and young adults. There is slight predilection for females[1,6,7].

Of the 160 splenectomies performed over an eighteen-year-period at the Hacettepe University Children's Hospital, three cases of cysts have been encountered, and only one of them was diagnosed as an epidermoid cyst.

Case Report

A sixteen-year-old girl with a history of intermittent pain in the left upper quadrant of the abdomen and left shoulder was examined at the Hacettepe University Children's Hospital. The pain which was unrelated to activity and unrelieved by food intake or antacids, was first noted three years ago. The patient had no history of previous trauma.

Physical examination was completely unremarkable. The hemoglobin level, leukocyte count, peripheral blood smear, platelet count, urinalysis, prothrombin time and liver function tests were all within normal limits. Roentgenograms of the chest and abdomen were also normal.

Ultrasound examination of the abdomen revealed a single cystic mass within the spleen measuring 6 ×8 cm. Computerized tomography confirmed the presence of the lesion (Fig. 1).

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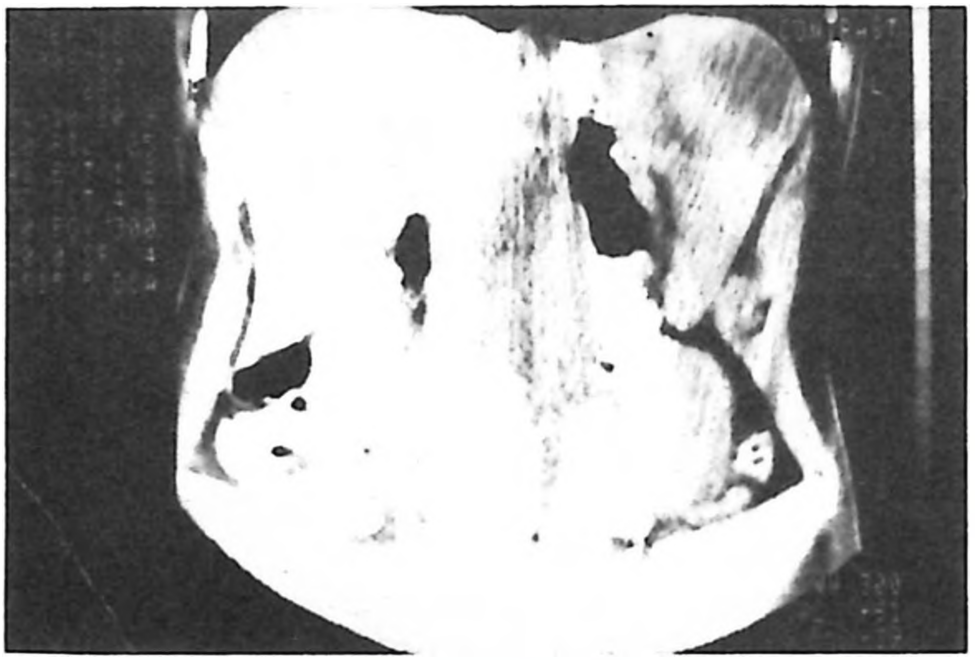

Fig. 1: Computerized tomography illustrating a single cystic lesion within the spleen.

Exploratory laparotomy performed showed no evidence of hydatid disease. A moderately enlarged spleen containing a large cystic lesion was found, and pale yellow, serous fluid was aspirated. Uninvolved splenic tissue could not be preserved due to an unsuitable vascular anatomy. A total splenectomy was performed. The postoperative course of the patient was uneventful.

Macroscopically, the multilocular cystic cavity revealed a thick, glistening, trabeculated fibrous capsule. The adjacent splenic tissue appeared normal (Fig. 2).

Fig. 2: Cut surface of the spleen showing trabeculated lining of the cyst (arrows indicate satellite cysts).

Histopathologically, the cyst was lined with stratified squamous epithelium with focal keratinization and no skin appendages. Several microcysts were present within the thick fibrous wall. A pathologic diagnosis made indicated epidermoid cyst of the spleen (Figs. 3A, 3B).

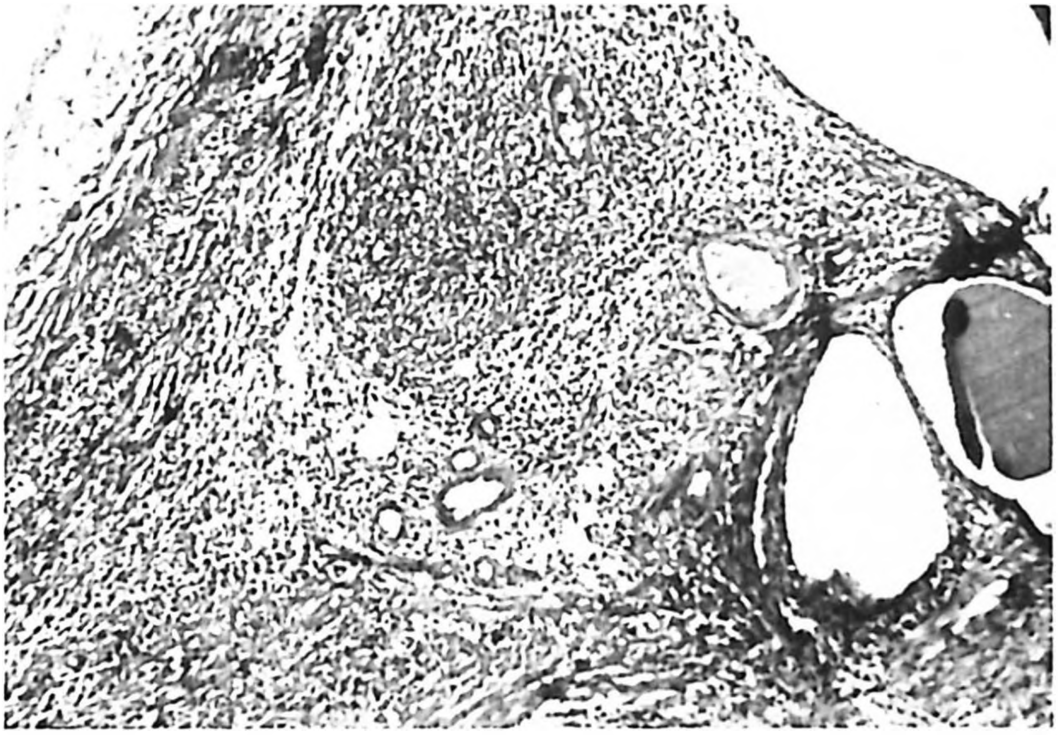

Fig. 3A: Multilocular cystic spaces and focal inflammatory reaction in cyst wall (H.E. × 100).

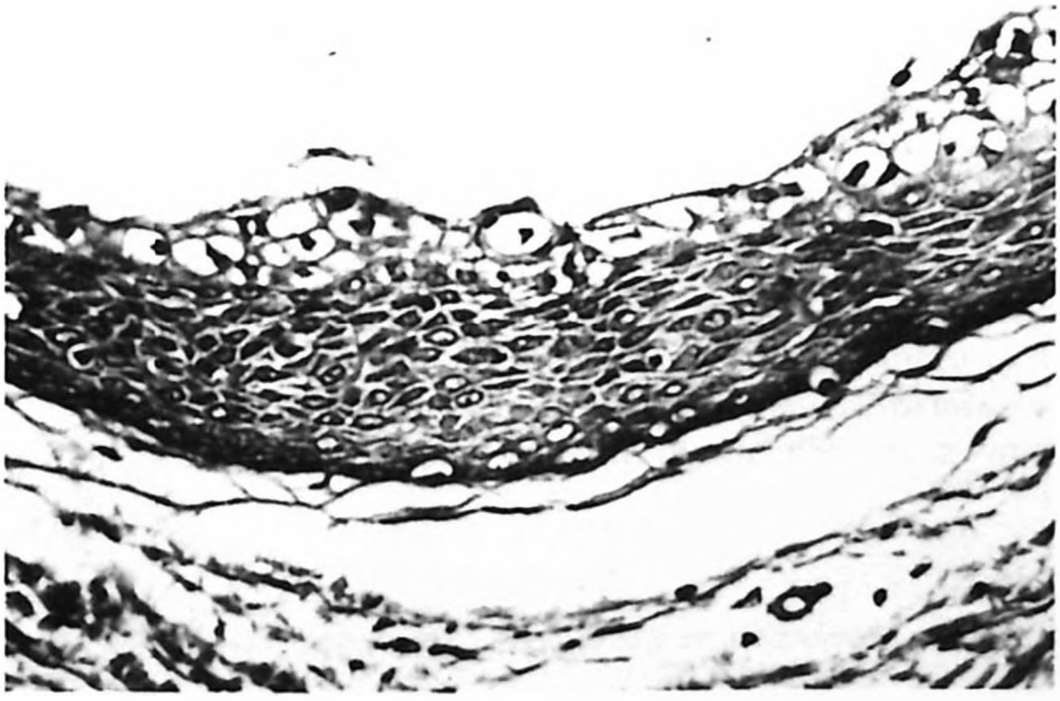

Fig. 3B: Epidermoid cyst lined by stratified squamous epithelium without skin appendages (H.E. × 400).

Discussion

The exact origin of epidermoid cysts are unknown[2]. However, most authors agree on the congenital nature of the lesion[2,7]. They are usually unilocular, and are sometimes accompanied by small satellite cysts, as in our case[2,8].

Symptoms in patients with splenic cysts are usually negligible. A vague, intermittent pain, generally described in the left upper quadrant and left shoulder is the most common presenting complaint. Large epidermoid cysts of the spleen predispose them to traumatic rupture and infection. Acute and severe symptoms are caused by hemorrhage.

Physical examination may be normal or reveal a left upper quadrant mass. Routine laboratory tests and roentgenograms are usually normal. In suspected cases, abdominal ultrasonography and computerized tomography are the most reliable studies for accurate preoperative diagnoses, and if they show a single cystic structure within the spleen, further invasive diagnostic studies such as selective splenic arteriography are unnecessary. However, epidermoid cysts are not distinguished preoperatively from other benign cystic tumors of the spleen. Most of the cystic lesions have been treated by total splenectomy. However, recently. some cases have been reported in the literature which were treated by partial splenectomy[4,7,9].

We believe that in order to prevent post-splenectomy sepsis, partial splenectomy should be preferred whenever possible. Since the splenic vascular distribution is easily visible during the operation, preoperative splenic arteriography is not necessary. However, total splenectomy may be unavoidable if there are large cysts occupying almost all of the spleen and/or inappropriate vascular tributaries, as in our case.

Summary

A sixteen-year-old girl treated by total splenectomy for epidermoid cyst of the spleen is presented. Epidermoid cysts of the spleen account for ten percent of non-parasitic cysts. Abdominal ultrasonography and computed tomography are the most reliable studies available in the diagnosis of these cysts. Partial splenectomy is the best mode of treatment for this disease, if feasible.

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The Turkish Journal of Pediatrics 31:239 - 244, 1989

NEPHROCALCINOSIS DUE TO VITAMIN D INTOXICATION*

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Key words: vitamin D intoxication, nephrocalcinosis

The toxic effects of excessive administration of vitamin D (Vit D) have been known for a long time. The characteristic features of Vit D toxicity were described in animals by Kreitmair and Moll[1] in 1928, and in the same year Hess and Lewis[2] reported clinical hypervitaminosis D in man. Since then, many reports on Vit D toxicity have been published concerning pharmacologic doses of this vitamin in the treatment of hypothyroidism, resistant rickets, renal osteodystrophy and overdosage in infants[2-9].

Hypercalcemia resulting from Vit D overdosage is a life-threatening condition which develops because of an increase in intestinal calcium absorption. Acute or chronic hypercalcemia may lead to the development of nephrocalcinosis by overloading the renal resorptive mechanism, and also to urolithiasis and soft tissue calcification[5,6,9-12].

The purpose of this study is to describe two cases of nephrocalcinosis caused by Vit D intoxication, review the clinical, biochemical, and radiologic findings of Vit D intoxication, and briefly discuss its treatment.

Case Report

Case 1

A three-month-old male infant was admitted to the Hacettepe University Children's Hospital with complaints of vomiting and lethargy of 10 days' duration. He had been treated twice previously for a diagnosed urinary tract infection. He had polyuria for the last 15 days. On further questioning, it was learned that Vit D had been administered to the patient in a dose of 45,000 IU/day for the last 45

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days. Physical examination revealed a subfebrile infant with a pulse rate of 144/min. The fontanel was slightly depressed (2 × 2 cm). Turgor and tonus were decreased. The infant, who seemed to be lethargic, had depressed eyeballs and dry oral mucosa. The other findings of the physical examination were normal.

Laboratory data revealed a hemoglobin level of 11.2 g/dl and a white blood cell count of 9,000/mm^3. The BUN was 10 mg/dl, HCO^-_3 27.96 mEq/lt, serum Na^+ 153 mEq/lt, K^+ 4.2 mEq/lt, calcium 19.5 mg/dl, phosphorus 2.6 mg/dl and alkaline phosphatase 3.6 BU. Urinalysis revealed hyposthenuric urine with a specific gravity of 1002, a trace amount of protein, no glucosuria and many leukocytes and calcium phosphate crystals in the urinary sediment. The urinary calcium/creatinine ratio was 1.3. Two consecutive urine cultures were found to be sterile. The urinary and serum amino acids were normal. Abdominal ultrasonography demonstrated bilateral medullary nephrocalcinosis (Fig. 1). No pathologic findings were seen on the IVP. A probable diagnosis of Vit D intoxication was made on the basis of the patient's clinical and laboratory findings and medical history. Treatment consisted of infusing 1/3 serum physiologic solution (3500 cc/m^2) and furosemide (4 mg/kg/day). A corticosteroid was also given (2 mg/kg/day) for 15 days. The patient was followed up closely for signs of dehydration and electrolyte imbalance. When the serium calcium level returned to normal, the infant was discharged with the recommendation of a high fluid intake.

Case 2

A four-month-old male infant was admitted to the Hacettepe University Children's Hospital with complaints of vomiting, lethargy and failure-to-thrive. He had had projectile vomiting for the last 10 days. It was noted that Vit D had been administered to the patient in a dose of 60,000 IU/day for the last month.

Physical examination revealed an afebrile infant with a pulse rate of 136/min and a respiratory rate of 34/min. The patient's general appearance and other findings of the physical examination were normal. Laboratory data revealed a hemoglobin level of 10.5 g/dl and a white blood cell count of 8,000/mm^3. The BUN was 14 mg/dl, serum calcium 17.6 mg/dl, phosphorus 3.8 mg/dl, alkaline phosphatase 10 BU, serum Na^+ 134 mEq/lt, K^+ 3.9 mEq/lt, and Cl^- 104 mEq/lt. Urinary examination revealed a specific gravity of 1002, trace amount of protein with 4-5 white blood cells per high magnification field in the urine sediment. Urinary culture yielded *E. coli* 10,000 microorganisms/ml but there were no microorganisms on a repeat culture. The urinary calcium/creatinine ratio was 0.7. There were no pathologic findings seen on the plain abdominal, and hand and wrist roentgenograms, or on the intravenous pyelogram. Abdominal ultrasonography revealed densely echogenic pyramids (Fig. 2). A probable diagnosis of Vit D intoxication was made on the basis of the patient's clinical, laboratory and radiological findings.

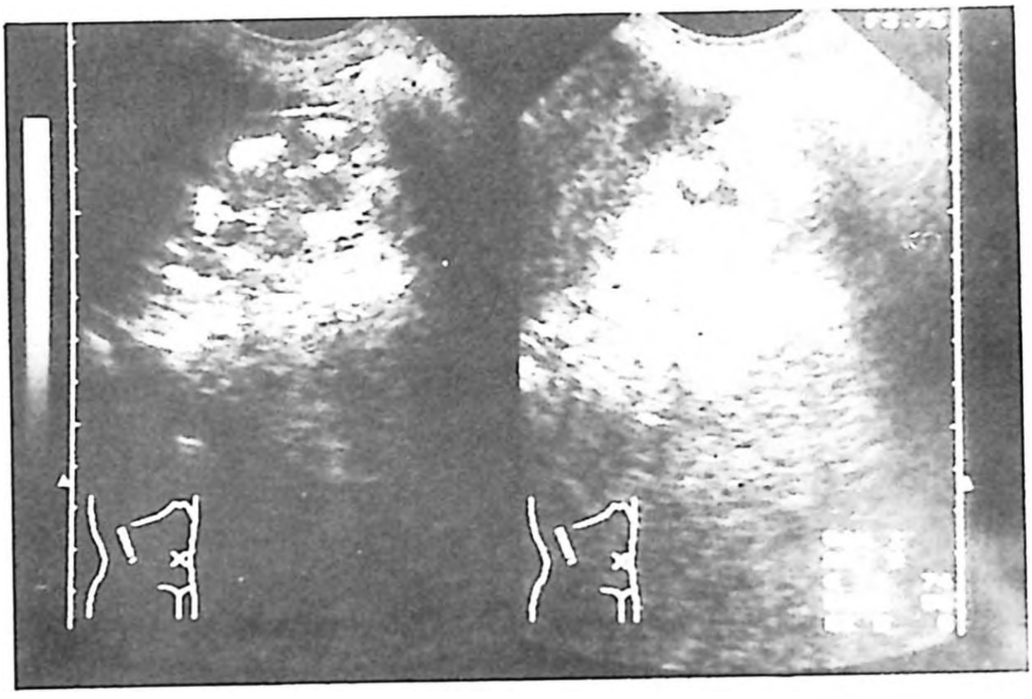

Fig. 1: Striking medullar nephrocalcinosis demonstrated during abdominal ultrasonographic examination.

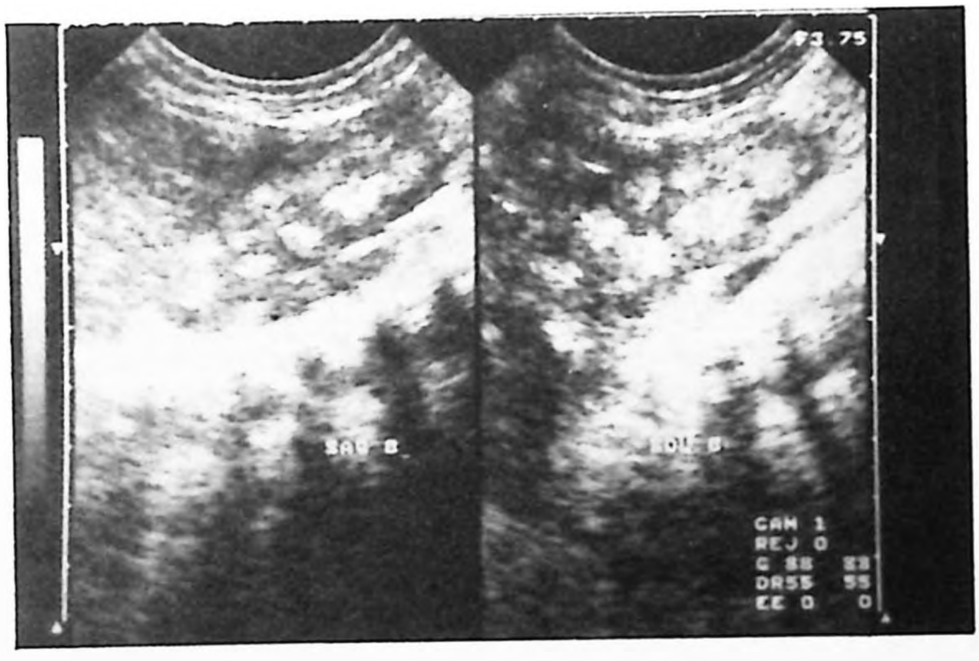

Fig. 2: The cortex of the kidney is normal. Medullary pyramids are seen as hyperechoic without acoustic shadowing.

The therapy initated was the same as for Case 1. When the serum calcium level returned to normal, the patient was discharged.

During the follow-up, the serum calcium and phosphate levels were normal, but the control ultrasonographic examination still showed medullary nephrocalcinosis six months after discharge.

Discussion

It is well known that pharmacologic doses of Vit D and a dose of over 400 IU/day in infancy results in Vit D intoxication[2-9,12]. Samir and Yazigi[5] reported fifteen cases of Vit D intoxication after the administration of 1.25 to 2 million IU of Vit D for a period of from one to four months. 30,000-60,000 IU/day of Vit D were administered to our patients for a period of from one to three months.

The typical manifestations of Vit D toxicity are attributed mainly to the resultant hypercalcemia. These include anorexia, failure-to-thrive, vomiting, constipation, irritability, convulsions, polyuria, polydipsia, dehydration and fever[5,9,12].

A potential renovascular effect of acute hypercalcemia leads to vasoconstriction in the renal arterioles which in turn decreases the glomerular filtration rate and the activation of the renin angiotensin system causes hypertension[9,12,13]. Our patients were admitted to the hospital with complaints of fever, vomiting, lethargy, dehydration and failure-to-thrive. Hypertension was not recorded in our cases. These findings were similar to the other cases reported.

The characteristic laboratory findings of Vit D intoxication are a high serum calcium level, normal or high serum phosphate level, and elevated alkaline phosphatase levels. Hypercalcemia resulting from Vit D intoxication is always associated with hypercalciuria[5,6,9,12]. Hypercalciuria is defined as urinary calcium excretion above 4 mg/kg/day or a urinary Ca/Cr ratio of the morning sample of over 0.21[9]. Hyposthenuric urine is frequently seen in cases of Vit D intoxication due to prepication of urinary calcium in the renal tubular cells. Hyposthenuric urine was also noted in our cases.

Hypercalcemia leads to nephrocalcinosis by overloading the renal resorptive mechanism[11]. A high calcium load causes cellular damage followed by calcium salt deposition in tubular cells, basement membrane epithelium, and within the loop of Henle. The classic distribution of nephrocalcinosis is along the corticomedullary junction[9-12]. Ultrasonography is superior to other radiological examinations with the exception of CT scanning[10,14] in demonstrating this type of abnormality. In our cases there were no pathologic findings on plain abdominal x-ray or intravenous pyelography. Ultrasonographic examination demonstrated medullary nephrocalcinosis.

Hypercalcemia also causes nephrolithiasis which is due to intratubular calcification and, less frequently, ectopic calcifications in the lung, heart, large vessels and skin, and band keratopathy in the cornea[9,12]. However, we did not observe such calcification in our patients.

Normal 1.25 $(OH)_2$ Vit D plasma concentrations have been reported in patients with hypervitaminosis D[15]. The diagnosis of Vit D intoxication is made by determining the serum 25-hydroxy Vit D (25-OH D) level[4,7,8]. In our cases, the 25-(OH) D level could not be measured.

The therapeutic approach to Vit D intoxication is symptomatic by putting the patient on a low calcium and Vit D-free diet, preventing exposure to the sun, and lowering the serum calcium levels[5,6,9,12,16]. Corticosteriods are used to prevent calcium reabsorption from the intestine and to increase calciuria[9,16]. Bromocriptine which is known to inhibit prolactin release, has been demonstrated to reduce serum calcium levels resulting from hypervitaminosis D in rats[17].

Furosemide-induced hypercalciuria is dependent on the natriuretic effect of this diuretic. After rehydration treatment, furosemide should be given until the serum calcium levels return to normal. Calcitonin is beneficial in cases of hypercalcemia accompanied by an acute decrease in neurologic, cardiovascular and renal functions[16].

Treatment in our cases consisted of rehydration with 1/3 serum physiologic infusion (3500 cc/m^2) followed by furosemide (4 mg/kg/day p.o) and prednisolone (2 mg/kg/day p.o) administration until the serum calcium levels returned to normal. During the follow-up period, the serum calcium levels were found to be normal, but the nephrocalcinosis persisted six months after discharge.

In the light of our experience with our two patients, the prescribed dose of Vit D should be carefully determined in order to prevent Vit D intoxication, and its complications. In addition, drug consumption without prescription, which is a big problem in developing countries, should be avoided.

Summary

Two cases of vitamin D intoxication are presented. The patients, one aged three months, and the other aged four months, were given Vit D in doses ranging from 30,000 IU/day to 60,000 IU/day for over a period of from one to three months.

Laboratory data showed serum calcium levels of 17.6-19.5 mg/dl and phosphorus levels of 2.6-3.2 mg/dl. Renal ultrasonographic examination demonstrated medullary nephrocalcinosis in both patients.

In this study the clinical, biochemical and ultrasonographic findings and the therapy of Vit D intoxication are reviewed, and preventive measures are suggested.

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The Turkish Journal of Pediatrics 31:245-247, 1989

MALIGNANT HYPERTHERMIA IN A PATIENT WITH SICKLE CELL ANEMIA*

*Aytemiz Gürgey MD***, Çiğdem Altay MD**, Saadet Özgen MD****

Key words: sickle cell anemia, malignant hyperthermia

Since as far as we know, there have been no previous reports in the literature describing the malignant hyperthermia syndrome (MHS) associated with sickle cell anemia, we decided to present a patient with sickle cell anemia who had developed malignant hyperthermia after receiving an anesthetic agent[1].

Case Report

A sixteen-year-old male with sickle cell anemia who had been seen at our hospital three or four times a year, had been experiencing painful crises over the last eight years.

Physical examination was unremarkable except for strabismus and the presence of hepatomegaly which was four cm below the right costal margin.

The hemoglobin level was stable at around 8 g/dl. The hemoglobin A_2 and hemoglobin F levels were two percent and nine percent, respectively. The remaining hemoglobin was Hb S. Both parents had Hb S traits.

At the age of sixteen, the patient was admitted to our hospital for surgical correction of strabismus. He was transfused until the Hb S level was fifteen percent. He was given succinylcholine and his temperature rose to 40°C within a few minutes, and surgery was cancelled. Cardiac arrest occurred, and the patient was resuscitated, cooled, and bicarbonate and prednisolone were administered intravenously. He recovered uneventfully within the following four to five hours. The serum creatinine phosphokinase level was found to be 18 units (normal: 8-12 units). A muscle biopsy revealed interstitial edema and a slight increase in fibrous tissue which were said to be characteristic of myopathy.

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Discussion

Malignant hyperthermia syndrome may develop after the use of general anesthetics such as succinylcholine and halothane[2,3]. This condition has been reported to be fatal in 20-40 percent of patients[4]. In some patients treatment with hydantoin derivatives has proven to be effective[3]. Our patient recovered within a few hours, without the administration of any specific form of therapy.

In half of the MHS cases an autosomal dominant form of subclinical myopathy has been observed. The presence of nonspecific musculoskeletal abnormalities such as ptosis or strabismus have been reported in one third of patients with MHS[5]. In addition, an elevated serum creatinine phosphokinase level has been found in some MHS patients with associated myopathy.

The association of MHS with pseudohypertrophic muscular dystrophy, the King syndrome, the Noonan syndrome, and a few malignancies have been reported[5-9]. In some cases virus-like particles have been observed in muscle biopsies, suggesting a viral etiology of the condition[10]. A slight increase in the serum creatinine phosphokinase level and changes in muscle biopsy associated with strabismus suggest the presence of an inherited susceptibility to MHS in our patient. Although there have been no reports in the literature describing a case of sickle cell anemia associated with MHS, it is still not clear whether malignant hyperthermia coincides with sickle cell anemia or if sickle cell anemia patients are susceptible to MHS.

Summary

A sixteen-year-old male with sickle cell anemia and congenital strabismus developed malignant hyperthermia a few minutes after the administration of succinylcholine, used as the general anesthetic for corrective eye surgery. The patient's hemoglobin S level was reduced to fifteen percent before the operation. He recovered uneventfully within a few hours. Increased serum creatinine phosphokinase activity and pathological changes observed in the muscle biopsy along with strabismus suggest that the patient had an inherited susceptibility to malignant hyperthermia.

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The Turkish Journal of Pediatrics 31:249 - 252, 1989

ANONYCHIA ASSOCIATED WITH ECTRODACTYLY SYNDROME: A CASE REPORT*

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Key words: anonychia, ectrodactyly

Anonychia associated with ectrodactyly is a rare congenital anomaly which is inherited as an autosomal dominant trait[1]. It was first described by Lees et al[2], in 1957. Ectrodactyly, which is the occurrence of bizarre digital anomalies, has also been noted to be associated with anonychia[2,3]. We report a patient with anonychia associated with ectrodactyly, who also presented with microcephaly.

Case Report

A two-month-old female infant was brought to the Pediatric Department of Erciyes University Hospital with anonychia and a deformed hand. She was the fourth child of healthy unrelated parents. The mother's history revealed no hereditary congenital anomalies. She had not been subjected to roentgenograms nor had she taken any medication during her pregnancy. The patient had two healthy brothers and a sister. The mother was unaware of anonychia in her or her husband's family.

Physical examination revealed an infant weighing 3950 g (10^{th} percentile), height 55 cm (10^{th} percentile), and head circumference 33 cm (below the 3^{rd} percentile). There was an absence of all nails except for the fifth nail of the left foot. Both her thumbs and great toes were shorter than expected. Moreover, she exhibited syndactyly between the fourth and fifth digits (Figs. 1 and 2). All other findings of the physical examination were unremarkable. Roentgenograms of the hand revealed an absence of the distal phalanges of the thumbs, and the distal parts of the other digits were not developed (Fig. 3). Craniosynostosis was not observed on the skull X-ray. Urine and blood amino acids were found to be within normal limits.

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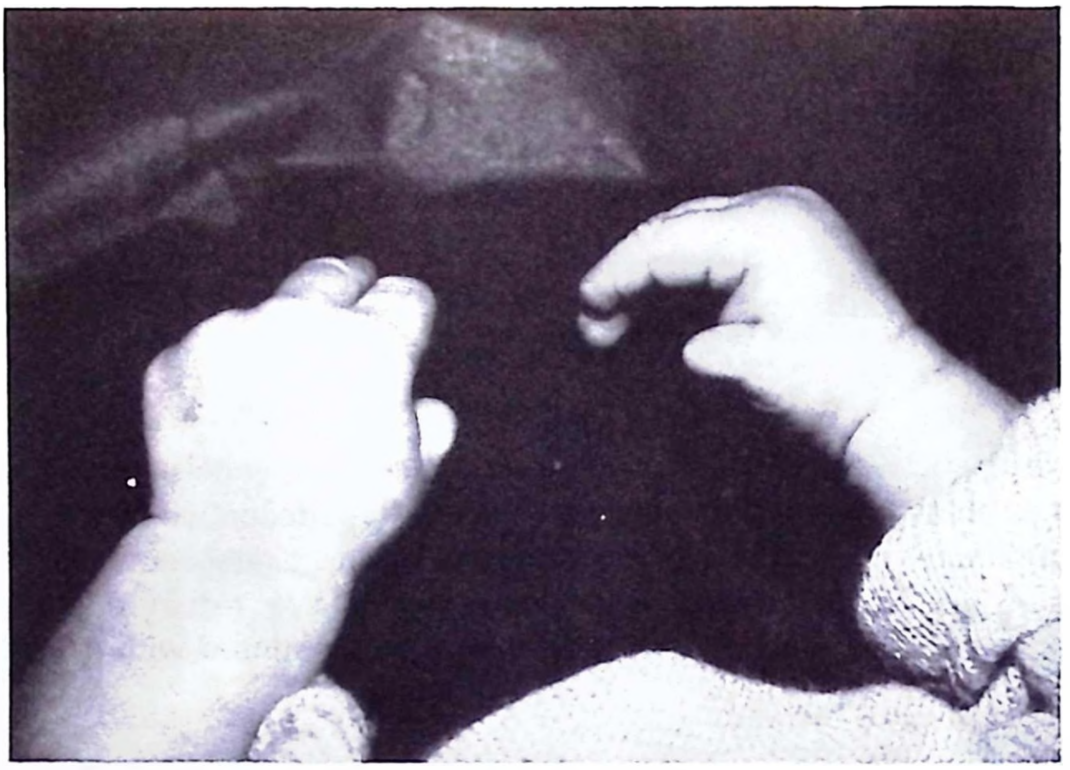

Fig. 1: The patient's hands showing ectrodactyly.

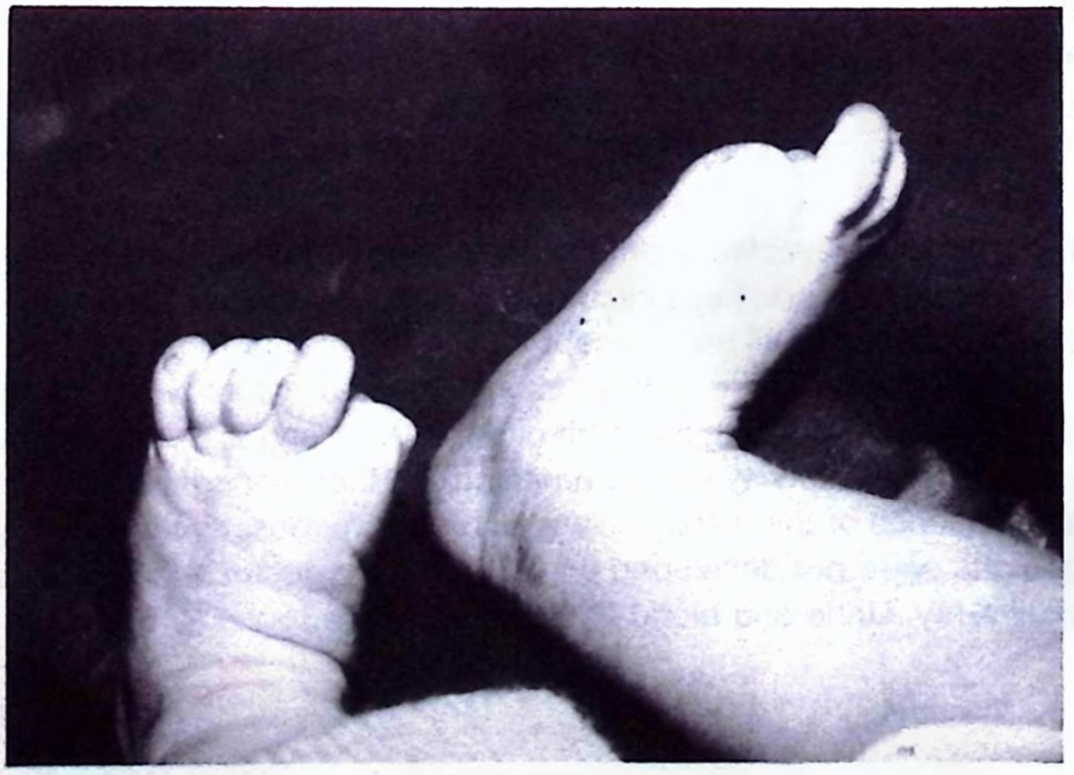

Fig. 2: The patient's feet showing anoncyhia with ectrodactyly.

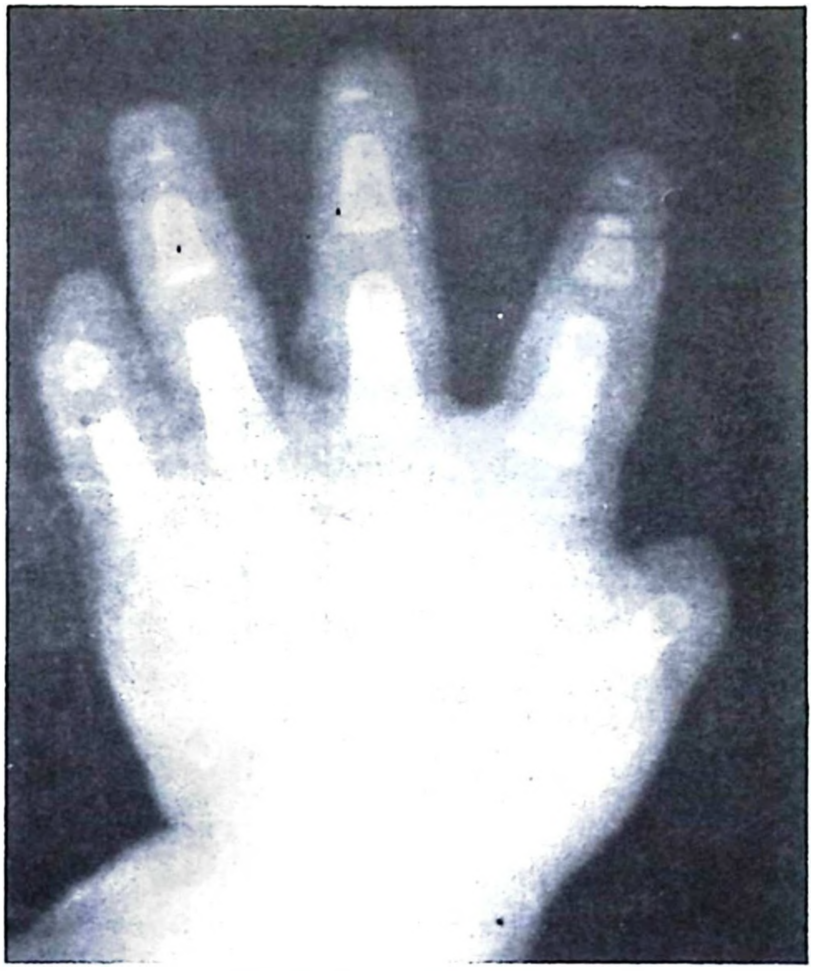

Fig. 3: X-ray of the hand.

Discussion

Cockayne[4] classified anonychia into four types: Type I, the most common, is characterized by a recessive mode of inheritance; Type II is transmitted on an autosomal dominant basis; Type III is characterized by an absence of thumb nails and red, sensitive nail beds, and Type IV comprises the nail-patella syndrome. In 1957, Lees et al[2] reported members of a large family having anonychia occurring with bizarre bony anomalies of the digits while Rahbari et al[5] reported a three-week-old boy with anonychia and associated ectrodactyly.

Our case was diagnosed as having anonychia associated with ectrodactyly since except for the fifth nail all the nails were absent on the left foot. In addition, the thumbs and great toes were shorter than they should have been. There was syndactyly between both of the patient's fourth and fifth digits. All these findings were supported by X-ray studies.

Even though this syndrome is inherited on an autosomal dominant basis[1,6], we were not able to find a case of anonychia with ectrodactyly in the patient's kindred, as had been reported by Rahbani et al[5] in his study.

Our patient was considered to be microcephalic since the head circumference was smaller than expected (below the 3rd percentile). However, the cause of microcephaly could not be determined by physical or laboratory findings.

In our search of the literature, cases of anonychia with congenital deafness or skin lesions have been reported but we could not find a case of anonychia with ectrodactyly and microcephaly. Our case of anonychia with ectrodactyly was coincidentally associated with microcephaly.

Summary

Anonychia with ectrodactyly is a rare inherited autosomal dominant syndrome. A case of a two-month-old female infant presenting with anonychia in association with ectrodactyly and microcephaly is presented.

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The Turkish Journal of Pediatrics 31:253 - 256, 1989

DO CERTAIN DRUGS CAUSE THE MEGACYSTIS-MICROCOLON-INTESTINAL HYPOPERISTALSIS SYNDROME*

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Key words: megacystis-microcolon-intestinal hypoperistalsis syndrome, maternal drug ingestion, malformations

The megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) was first described by Berdon et al[1] in 1967. Since then an increasing number of cases with this congenital abnormality has been reported in the literature[2-11]; they all describe this disease as a syndrome of unknown etiology.

Last year, we reported the case of a baby with the megacystis-microcolon-intestinal intestinal hypoperistalsis syndrome who was the product of a mother who had taken clomiphene during pregnancy[12]. I have recently seen another MMIHS case in an offspring of a mother who had taken scopolamine, dipyrone and trimethoprim-with-sulfamethoxazole in the first month of pregnancy. This second instance of the same abnormality associated with drug intake during pregnancy encouraged me to explore the possibility of a relationship between maternal drug ingestion and MMIHS.

Case Report

A baby girl of 40 weeks' gestational age weighing 2,600 g was born on January 17, 1988 to a 23-year-old mother. On April 21, 1987, her mother was prescribed talcid (hydrotalcit 1500 mg × 30 days), Buskaljin^{R} (hyoscine-N-buthyl bromide 30 mg: natrium methyl-amino-phenyl-dimethyl pyrazolon methane sulfonate 750 mg × 30 days) and Sulfatrim^{R} (trimethoprim 180 mg, sulfadiazine 820 mg 15 days) for gastrointestinal discomfort and urinary infection which she had taken regularly during the first month of pregnancy.

Immediately after delivery, the infant's abdomen appeared markedly distended. Bile-stained material was suctioned from the stomach.

Spontaneous micturition occurred but no defecation was observed until fifteen hours after delivery. Auscultation detected silent abdomen. Abdominal ultraso-

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nography revealed peritoneal fluid and hyperechoic areas due to distension of the bowels. Roentgenograms showed intestinal obstruction, and barium enema examination failed to demonstrate beyond the rectum.

At the twentieth hour an exploratory laparotomy was performed which revealed all the classical findings of megacystis-microcolon-intestinal hypoperistalsis syndrome (Figs. 1, 2). This was terminated in surgery.

Sepsis developed postoperatively, and the patient died on the fifth day after the operation. Her parents did not give permission for an autopsy.

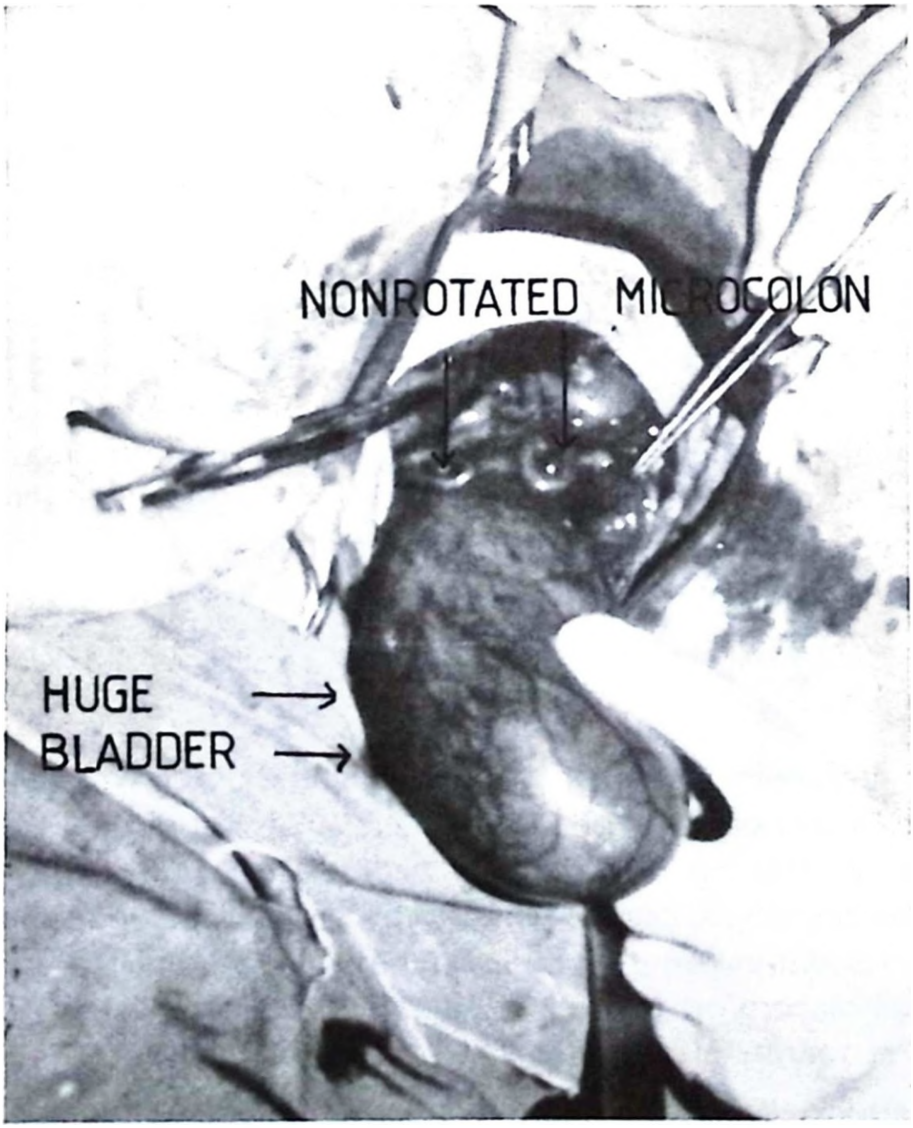

Fig. 1: Operative view of the case revealing a hug bladder and nonrotated microcolon.

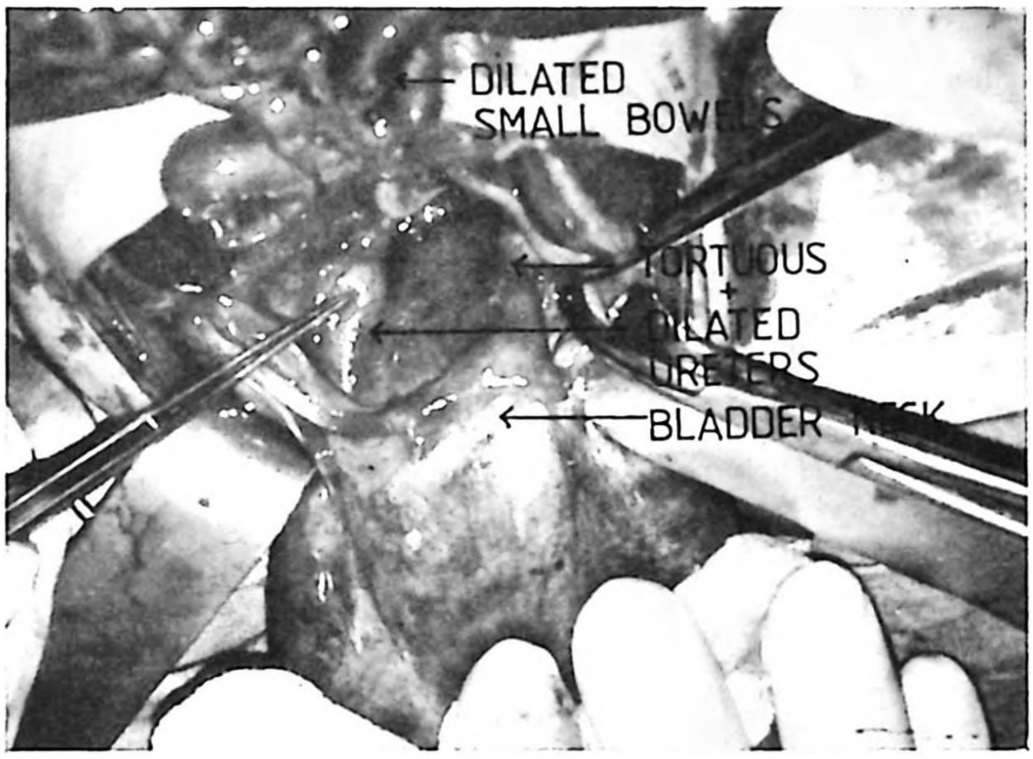

Fig. 2: A close-up view of the same area: tortuous, dilated ureters and dilated small bowels are seen.

Discussion

In previously reported cases of MMIHS great importance was given to the antenatal ultrasound appearance and histopathological examination of the bowel and urinary bladder[1,3,5,9] but as of yet there has been no mention of a relationship existing between maternal drug ingestion and MMIHS.

In our first case, the mother of the baby was given clomiphene citrate (50 mg × 5 days) for two cycles and became pregnant at the end of the second cycle. Clomiphene has been widely accepted as a drug having a possible teratogenic effect, and some congenital abnormalities have been reported in both clomiphene-induced pregnancies and the babies who had been exposed to the drug during pregnancy[13,14]. We therefore present this case as another instance of congenital anomalies associated with maternal clomiphene treatment[12]. However, a causal relationship between MMIHS and maternal clomiphene ingestion has not yet been established.

There are several reports in the literature describing congenital defects in the offspring of mothers who had taken trimethoprim-sulfadiazine[15], and scopolamine derivatives[16] during pregnancy. Dipyrone, a methane sulfonate derivative of amiopyrine has disappeared from the therapeutic scene in most countries because of its potentially fetal toxicities[17]. Pharmaceutical companies recommend that these drugs should not be used during pregnancy. It must be stressed, however, that without performing any experimental studies, it is very difficult, and even impossible, to prove whether these drugs cause malformations. However,

the second instance of the same abnormality associated with maternal drug ingestion led to the formulation of the hypothesis: "Do certain drugs cause the megacystis-microcolon-intestinal hypoperistalsis syndrome?".

Summary

A case of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) in the offspring of a mother who had ingested scopolamine, trimethoprim-sulfadiazine and dipyrone during pregnancy is presented. In order to determine whether a relationship exists between maternal drug ingestion and MMIHS, the need for further experimental studies is stressed.

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