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AMYLOIDOSIS IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER*

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Familial Mediterranean fever (FMF) is a heredofamilial disease that occurs predominantly in patients of Mediterranean, Eastern European, or Middle East origin, particularly Sephardic or non-Ashkenazic Jews, Armenians, Arabs, and Turks. This autosomal recessive disorder of unknown etiology is characterized by recurrent episodes of fever associated with serositis of the peritoneum and pleura, and arthritis.[1-3] An erythematous rash may also rarely occur. Familial Mediterranean fever is the cause of secondary amyloidosis. Since the disorder occurs frequently in Turkey, renal histopathological changes are looked for if nephrotic syndrome or proteinuria develops in a case with FMF and in all cases with nephrotic syndrome and proteinuria. [1-13]

The purpose of this report is to describe the clinical features and laboratory findings of 113 children with amyloidosis and to determine the benefical effects of colchicine as treatment for the disease.

Material and Methods

The survey included 113 subjects with amyloidosis secondary to FMF who had been admitted to the Departments of Pediatric Nephrology at Hacettepe University Hospital, and Ondokuz Mayıs University Hospital, from 1975 to 1986. There were 65 boys and 48 girls.

The diagnosis was established by the characteristic clinical findings of FMF such as fever, peritonitis and arthritis, and by the evaluation of renal biopsy specimens obtained from all patients. Those with either clinical or laboratory evidence of rheumatoid arthritis, chronic suppurative diseases or polyneuropathic familial amyloidosis were excluded from the study.

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The subjects were classified into two groups:

— Phenotype I: FMF episodes precede the development of amyloidosis.

— Phenotype II: Manifestations of amyloidosis precede FMF episodes or patients not living long enough for an attack to develop.

All patients were advised to follow a diet rich in protein. Salt intake was only restricted in edematous patients. All patients were treated with colchicine in a dose of 1.5-2 mg per day. The doses were determined according to the patient's tolerance.

Results

Sixty-five boys and 48 girls whose ages ranged between four to 17 years (mean 12.02 ± 3.12 years) were included in the study (Fig. 1). The male: female ratio was 4/3.

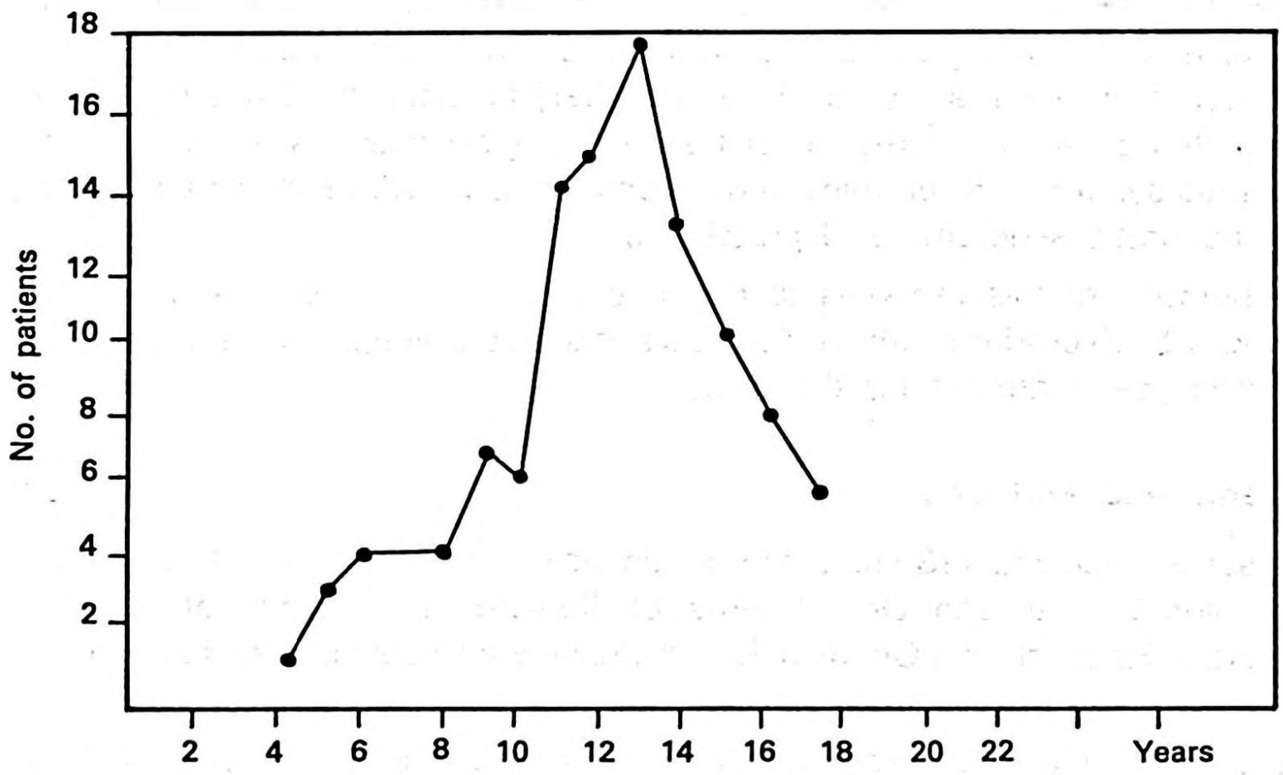

Fig. 1. Age distribution of patients (Yrs)

The patients were followed up for a mean period of 27 months (2-87 months). Most of our cases (84 patients, 74.33 %) demonstrated phenotype I characteristics while the others (29 patients, 25.67 %) phenotype II characteristics.

In phenotype I subjects, amyloidosis developed in a period of from two months to 14 years after the onset of periodic attacks.

As seen in Table I, fever is the most common feature of the disease. Episodes of abdominal pain and arthralgia were seen in one third of the patients. Only 24 patients had a positive family history for the disease.

The children were reexamined at least once, and we observed that all the symptoms occurring during the attacks were relieved by colchicine therapy. Eleven patients treated with colchicine (aged 11-13 years), who were followed up for 27-63 months, showed no signs of renal failure. Their growth rate was 4-6.5 cm per year.

The mean arterial systolic pressure was 107.71 ± 14.7 mmHg, and the diastolic pressure 69 ± 1.3 mmHg. During the follow-up period hypertension was noted in only five cases with renal failure.

Forty cases (35.39 %) had hepatomegaly (1-8 cm), and 14 cases (12.38 %) splenomegaly (1-9 cm).

Clinical and laboratory findings are shown in Tables I and II.

Table I: Clinical Features of Amyloidosis in 113 Children With Familial Mediterranean Fever.

	Number of Findings / Total Case (%) Number
Family history	24/113 (21 %)
Phenotype 1	84/113 (74 %)
Phenotype II	29/113 (26 %)
Fever (periodic)	68/84 (75 %)
Abdominal attacks	35/84 (41 %)
Arthritic attacks	34/84 (40 %)
Hepatomegaly	40/113 (35 %)
Splenomegaly	14/113 (12 %)
Hypertension	5/113 (4 %)
Renal failure	22/113 (19 %)

Table II : Laboratory Findings of Amyloidosis in 113 Children With Familial Mediterranean Fever.

	No. (%)
Anemia	34 (30 %)
Leukocytosis	55 (49 %)
Hypoalbuminemia	66 (58 %)
Hyperuricemia	30 (27 %)
Prolonged PT*	7 (7 %)
Prolonged PTT**	96 (85 %)
Hyperlipidemia	48 (42 %)
Hypercholesterinemia	84 (74 %)
Hematuria	29 (26 %)
Leukocyturia	42 (37 %)

PT* :prothrombin time; PTT** :partial thromboplastin time.

As seen in Table III, there was no significant statistical difference found between the hemoglobin, serum globulin, cholesterol, lipid and daily urinary protein excretion values before and after colchicine therapy. However, a significant difference was seen between the serum total protein and albumin values.

Table III- Some Laboratory Findings Before and After Colchicine Therapy.

	Before colchicine therapy (mean values)	After colchicine therapy (mean values)	P values
Hemoglobin (g/dl)	11.32±2.13	10.90±2	p>0.05
Total serum protein (g/dl)	4.73±0.99	5.01±1	p<0.01
Serum albumin (g/dl)	2.4±0.87	3.3±0.5	p<0.01
Serum globulin (g/dl)	2.29±0.60	2.3±0.7	p>0.05
Daily urinary protein (g/24hr)	2.65±2.12	2.69±1.9	p>0.05
Total serum lipid (mg/dl)	1098±381	1150±300	p>0.05
Serum cholesterol (mg/dl)	290±132	140±86	p>0.05

Discussion

FMF is characterized by recurrent attacks of fever accompanied by signs of peritonitis and/or pleuritis. Some patients may also have arthritis and skin lesions. The term "Familial Mediterranean fever" is suitable because many of those affected by the disease are of Mediterranean origin i.e., non-Ashkenazic Jews, Turks, Italians and Greeks.[1-3]

As is shown in Fig. 1, the number of patients with amyloidosis increased through out the adolescent period during which time the attacks of FMF were frequently encountered.

While there is no registry centre, as far as we know, the number of cases with amyloidosis secondary to FMF in our survey is the largest yet presented. In our group, 24 patients (21.23 %) had a familial history of FMF, which is a ratio lower than expected[3,9-13]. One of the most important characteristics of amyloidosis secondary to FMF is that it may be seen initially without showing any clinical signs of FMF, phenotype II. Even if there is preventive treatment in the future for secondary amyloidosis due to FMF, there will still be a problem for phenotype II cases. As seen in Table I, the incidence of phenotype II was high, even though it is mentioned as a rare variant.[3]

Although it is not possible to predict when amyloidosis formation occurs in FMF, it generally takes from four to ten years.[1,3,5,11-15]. Because FMF cases develop

according to the phenotype I or II classification there are really great differences between the appearance of amyloidosis and the onset of FMF attacks.[12-14] In fact, in our phenotype I cases there had been recurrent attacks for a period of from two months to fourteen years before amyloidosis developed or was diagnosed.

Symptoms of periodic attacks according to frequency in phenotype I patients were fever (25 %), abdominal pain (41 %), and arthritic attacks (40 %). As seen in our patients, fever in FMF has frequently been the presenting sign together with other findings (Table I). Abdominal and synovial attacks reported in the literature, as 95 and 75 percent, respectively were seen less frequently in our study.[3,9,10]

All our cases with FMF attacks were examined at least once, and it was observed that periodic attacks could be relieved by colchicine. Our results also support the argument that colchicine may be used as a drug to diagnose FMF.[4,16-27]

Out of 113 patients, only five presented with hypertension. These hypertensive cases were those who had been followed up for one–three years. The general opinion is that these subjects may have had hypertension during the period of end stage kidney disease because of kidney shrinkage. Reports in the literature state that the proportion of hypertensive cases at the end-stage period may reach 20-30 percent[3,12,13]. It is commonly considered that amyloidosis generally results in hypotension because of adrenal involvement.

Our patients had hepatomegaly (8 cm) and splenomegaly as well; only two cases with splenomegaly did not evidence hepatomegaly.

In the cases without renal failure, obvious anemia was not seen. Only 34 cases (30 %) had mild anemia (Table II). While it has been suggested that anemia is not a common finding in amyloidosis, it generally appears in the uremic stage of the disease[1,3,11,13]. In the cases with slight anemia, this finding was not due to the colchicine administered. Leukocytosis was not an important finding; it was present in only fifty-five subjects, the others were normal.

Sixty-six patients had severe hypoalbuminemia. This condition was encountered in a patient who manifested a serum albumin value as low as 0.7 g/dl. We noticed that there were increasing serum total protein and serum albumin values in the cases treated with colchicine but that there were no changes in the serum globulin values.

We concluded that the increase in the values of serum total protein and albumin of the patients on colchicine could depend partly on good patient care, i.e, a good diet, amino acid tablets and also partly on the beneficial effect colchicine has on amyloidosis. There was only one case in which proteinuria had disappeared over a period of two years while the patient was receiving colchicine. However, with the

cessation of the drug by the patient, FMF findings and proteinuria reappeared. Some observations have suggested that amyloidosis associated with FMF could be put into full remission with colchicine[25].

Another important finding in 96 (84.95 %) of the cases that we followed was that the PTT had increased (Table II) which is an important observation for secondary amyloidosis. Despite the significant amount of amyloid deposition in the liver, alterations in hepatic function were generally considered to be minimal. An increase in the level of PTT is an early and important indication of liver dysfunction assisting a clinical evaluation of amyloidosis[1,3,7]. The serum uric acid level was high in nearly 25 percent of the cases, while the serum cholesterol and lipid concentrations were high in 75 percent of the patients. There was a correlation between hypercholesterinemia and hyperlipidemia. But we were not able to find any changes in the serum lipid and cholesterol levels in the cases treated with colchicine.

Summary

In this survey 113 children with secondary amyloidosis due to familial Mediterranean fever are reviewed in regard to their respective histories, and physical and laboratory findings. The benefical effects of colchicine in the treatment of this condition are evaluated. The number of children presented with amyloidosis secondary to familial Mediterranean fever was considerable. The male-female ratio was 4/3. It was observed that the number of patients with amyloidosis increased through the adolescent period, and that most of the cases demonstrated phenotype I (74.33 %). Another important finding was the increase of partial thromboplastin time in 96 out of 113 cases (84.95 %). All the symptoms of the periodic attacks were relieved by colchicine. A significant difference was found between the serum total protein and albumin values before and after colchicine therapy.

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