Amyloidosis in children with familial Mediterranean fever

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SUMMARY The clinical and laboratory findings of 35 children with familial Mediterranean fever who developed amyloidosis are described. The types, frequency, and severity of attacks of familial Mediterranean fever in these children were no different from patients with this disease without amyloidosis. Although amyloid was widely deposited in all tissues, the major clinical manifestations of the amyloidosis were proteinuria, the nephrotic syndrome, and progressive renal failure. Only 20% of the patients were alive 5 years after the first appearance of proteinuria.

Amyloidosis is rare in children.¹ Although its pathogenesis is unknown, the classification of primary and secondary amyloidosis is widely used. In the former, amyloidosis occurs as part of a genetic syndrome, usually with major involvement of the peripheral nervous system and the heart.² The associated diseases in secondary amyloidosis in childhood are juvenile rheumatoid arthritis, chronic infections, and familial Mediterranean fever (FMF).

In Israel FMF is a common genetic disease because of its high prevalence in the Sephardic Jewish community.* This disease occurs almost exclusively among Sephardic Jews, Armenians, and Arabs originating in the Levant.³ The disease is characterised by recurrent attacks of fever, associated with serositis affecting the peritoneum, pleura, and large joints. Rarely an erythematous rash occurs. These attacks reach a peak within 24 hours and then generally regress during the next 2 to 4 days. The acute episodes of the disease are indistinguishable from peritonitis, pleuritis, and arthritis, so the diagnosis is often made only on the basis of the recurrent nature of the illness and the family history. Recently colchicine was shown to reduce the frequency and severity of attacks.^{4 5}

The purpose of this report is to describe the clinical features of 35 children with amyloidosis. All of them had FMF, and have been seen during the last 20 years at one hospital in Israel.

*The Sephardic Jews originated from several Mediterranean countries and Iraq. They comprise about half of the population in Israel.

Materials and methods

The case records of all inpatients during the period 1955-75, aged <15 years, with a diagnosis of amyloidosis were reviewed. There were 16 boys and 19 girls. The criterion for diagnosis was the positive identification of amyloid by rectal or renal biopsy, or at necropsy.

Amyloid was identified histologically by a Congo red stain as a green material when viewed with a birefringent light. The indication for biopsy in these patients with FMF had been the appearance of persistent proteinuria. (The proteinuria was considered to be the first clinical sign of amyloid affecting the kidney.)

Results

The clinical features of FMF in patients with amyloidosis were no different from those in patients without it. In none of them did signs of amyloidosis precede those of FMF. Abdominal attacks were the most common clinical feature; however, in most patients, at some time in the course of the disease, both joint and pleuritic involvement were encountered, either conjointly or separately. The diagnosis of FMF was made on clinical grounds and no single laboratory investigation was specific for the disease. However, fibrinogen levels and erythrocyte sedimentation rates were always raised during the attacks. Anaemia (haemoglobin <10 g/dl) was found in 22 patients. Leucocytosis was absent (Table 1).

Table 1 Clinical and biochemical features of familial Mediterranean fever in 35 children

	No	%
Abdominal attacks	34	97
Arthritic attacks	24	71
Skin manifestations	4	14
Anaemia	28	80
Raised erythrocyte sedimentation rate	35	100
Raised fibrinogen levels	30	86

The age of onset of FMF and that of amyloidosis is shown in Fig. 1. Twenty-two patients had signs of FMF within the first 5 years of life. Patients who developed amyloidosis at a very early age did not have an increased frequency or severity of attacks. The interval between the age of onset of FMF and that of amyloidosis varied.

The major site of organ involvement of amyloidosis in FMF was the kidney. All the patients had proteinuria, and 30 had the nephrotic syndrome at sometime during the course of the disease. All except one died of chronic renal failure. The course

of the disease from the appearance of proteinuria to chronic renal failure was rapid (Fig. 2). Hypertension was noted in only 4 patients. Hepatosplenomegaly was common, but liver function tests were only slightly disturbed in a few patients. A neuropathy was not seen in any patient (Table 2).

The diagnosis of amyloidosis was confirmed histologically in 33 patients. Two patients, who died of renal failure, had negative rectal biopsies and since no necropsy was performed, they have been considered probable cases. Renal biopsy was performed in 12 patients and was positive in all. Rectal biopsy which was performed by a suction apparatus, was a benign procedure with no discomfort to the patient and was positive in 25 of the 30 patients on whom it was done. In this series no bleeding or other complication was encountered after biopsy.

Necropsy was performed in 13 patients. All had severe amyloid involvement of the kidney: 6 had

Fig. 1 Age of onset of familial Mediterranean fever compared with that of amyloidosis.

Fig. 2 Actuarial survival curve of 35 children with amyloidosis and familial Mediterranean fever.

Table 2 Clinical features of amyloidosis in 35 children with familial Mediterranean fever

	No	%
Proteinuria	35	100
Nephrotic syndrome	30	87
Chronic renal failure	32	89
Hepatomegaly	27	77
Splenomegaly	27	77
Hepatosplenomegaly	25	71
Hypertension	4	14

obvious infiltration of the liver and spleen, 4 had amyloidosis of the heart, and 1 patient had extensive involvement of the gastrointestinal tract. The amyloid was distributed in a typical perireticular pattern.⁶

All the patients were of Sephardic Jewish origin. The parents were 1st-cousins in 4 families. There were 4 sibling pairs with FMF and amyloidosis, and in them the age of onset and progress of disease was similar. In addition 9 patients each had one sibling who had FMF with no signs of amyloidosis. Genetic analysis was performed in 17 families in whom a complete history of the sibship was available. In these families there were 29 affected and 63 unaffected siblings. Six of the affected patients had FMF only, without evidence of amyloidosis. The corrected ratio of affected to unaffected siblings was 0.257 (variance 0.003), which is consistent with an autosomal recessive mode of inheritance.⁷

Discussion

Amyloid is an amorphous, fibrillar, eosinophilic, extracellular material which produces its clinical effects by compression of normal tissue. In secondary amyloidosis the liver, spleen, kidneys, adrenals, and heart are generally affected. Except for the patients with cured chronic infections and rare instances of juvenile rheumatoid arthritis,⁸ amyloidosis tends to be relentlessly progressive because of the persistence of the primary disease. Renal failure is the most common cause of death and there is generally little clinical dysfunction of the other organs.⁹

Amyloidosis has been recently divided into two major types by virtue of the chemical structure of the deposits. In macroglobulinaemia, multiple myeloma, and the primary genetic amyloidoses, part of the amyloid deposit is made up of the variable component of the light chain of an immunoglobulin molecule; whereas in amyloidosis associated with chronic infections, rheumatoid arthritis, Hodgkin's disease, and FMF the amino-acid sequence is identical,¹⁰ but no immunoglobulin fragment is present. Interestingly, this clear chemical definition corresponds to the earlier histological classification of amyloid to either a pericollagenous or perireticular deposition.⁶ Although several experimental studies suggest that the pathogenesis of amyloidosis is immune-mediated, the precise role of abnormal cellular or humoral function is unclear.^{11,12} In addition immunopathological mechanisms are implicated in most types of secondary diseases which cause amyloidosis.

In the first two decades of life about one-third of all the patients with FMF developed amyloidosis.³

The onset of amyloidosis in children with FMF heralds a poor prognosis. Renal involvement is the most important complication and is first manifest by proteinuria. Generally the nephrotic syndrome develops during the course of the disease and most children die of chronic renal failure within 5 years. Hypertension is conspicuously absent. Amyloidosis in juvenile rheumatoid arthritis is less common than in FMF; however, the course of the disease is less rapid.⁹ Although the appearance of proteinuria in a patient with FMF strongly suggests the presence of amyloidosis, it should be confirmed by rectal biopsy.¹³ The demonstration of Congo red staining fibrils in the urine is not pathognomonic of renal amyloidosis.¹⁴

Rare instances of the clinical features of amyloidosis preceding those of FMF have been reported and classified as a separate phenotype of FMF.⁶ However, all our patients developed amyloidosis after the onset of FMF and there were no differences in the clinical or laboratory features of the patients with FMF who developed amyloidosis, and those who did not. It is not known whether the presence of amyloidosis in patients with FMF occurs as a complication of FMF or is part of a genetically-determined syndrome. Further delineation of the inborn error of metabolism of FMF will probably resolve these questions.

Attempts to treat amyloidosis by immunosuppression,^{15,16} steroids,^{17,18} and fat elimination diets¹⁹ have been unsuccessful. Kidney transplants have been performed in patients with amyloidosis, but recurrence of amyloid in the transplanted kidney has been reported.^{20,21} Complications of amyloid involvement of other organs, especially of the heart, may be encountered if life is artificially prolonged. In addition a limited follow-up study of 5 patients with renal amyloidosis who received adequate treatment with colchicine, in addition to immunosuppressive drugs, after renal transplants, showed no recurrence of the disease.²² Colchicine has been used extensively with great success for the prevention of the 'attacks' of FMF.²³ It has also been shown to inhibit the development of casein-induced amyloidosis in mice.^{24,25} It has been reported to alleviate the nephrotic syndrome in patients with amyloidosis and FMF.²⁶ Perhaps, the onset of amyloidosis will be prevented or delayed in patients with FMF treated with colchicine.

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