Nephrol Dial Transplant (2002) 17: 2003–2005

Nephrology
Dialysis
Transplantation

Brief Report

A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey

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Abstract

Background. Secondary amyloidosis is the most frequent of the various types of systemic amyloidosis, the epidemiology of which is not yet fully known. The aim of our study was to evaluate retrospectively the collective data for the aetiological distribution, clinical findings and approaches to the management of secondary amyloidosis in Turkey.

Methods. Data from a simple questionnaire addressing aetiology, and demographic and clinical characteristics of patients with biopsy-proven secondary amyloidosis was retrospectively analysed. Eleven nephrology clinics contributed data for this study.

Results. The 11 contributing centres provided a total of 287 cases (102 female, 185 male). The aetiological distribution was as follows: familial Mediterranean fever (FMF) 64%, tuberculosis 10%, bronchiectasis and chronic obstructive lung disease 6%, rheumatoid arthritis 4%, spondylarthropathy 3%, chronic osteomyelitis 2%, miscellaneous 4%, unknown 7%. Oedema accompanied by proteinuria was present in 88% of the cases, hepatomegaly in 17%, and splenomegaly in 11%. The mean systolic and diastolic blood pressures were 115 ± 26 and 73 ± 15 mmHg respectively. The family history was positive in 16%; 73% of the cases were on colchicine treatment when the questionnaire was administered. Thirty-eight per cent of the cases had progressed to ESRD and were on renal replacement therapy.

Conclusions. FMF is the leading cause of secondary amyloidosis in Turkey, followed by tuberculosis. Oedema accompanied by proteinuria is the most prominent presenting finding, and hypotension seems to be common among these patients.

Keywords: aetiology; amyloidosis; clinical findings; end-stage renal disease; family history

Introduction

Amyloidosis is a disease of protein metabolism characterized by the deposition of fibrillar proteins in various organs. The aetiology of systemic amyloidosis is multifactorial, and primary or secondary (reactive) types have been defined [1]. Secondary amyloidosis is the most frequent type of systemic amyloidosis, with a prevalence varying between 0.5 and 0.86% in different series of autopsies [2]. Since the clinical manifestation of AA amyloidosis is dominated by nephropathy, it has been of major interest to practicing nephrologists. We report the aetiological distribution in 287 cases of renal amyloidosis from 11 nephrology centres in Turkey, along with the clinical findings at presentation and current approach to management.

Subjects and methods

A questionnaire was sent to 18 nephrology clinics in Turkey, two of which were paediatric units; 11 centres (61%) responded. The biopsies available for our cohort were evaluated at each of the responding centres by nephropathologists

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experienced in amyloidosis. The pathological diagnosis of amyloidosis was made on Congo red stained biopsy specimens, and the distinction between AA (secondary) and AL (primary) amyloidosis was made by immunohistochemical staining. The questionnaire was simple, covering the demographic characteristics of the patients including age at presentation, gender, family history of amyloidosis and aetiology of amyloidosis, presence of oedema, hepatomegaly and splenomegaly, systolic and diastolic blood pressures. Hepatomegaly or splenomegaly must have been established by physical examination and confirmed by abdominal ultrasound examination. The presence of end-stage renal disease (ESRD), other organ involvement and the type of treatment, including colchicine, were also elicited by the questionnaire. The collected data were analysed using Accutest for descriptive statistical analysis.

Results

A total of 293 cases of biopsy-proven amyloidosis were reported from 11 centres, but only 287 cases of secondary amyloidosis—102 females (35%) and 185 males (65%)—were evaluated (six cases with AL amyloidosis were excluded). The mean age of the patients at presentation was 29 ± 18 years (F 26 ± 17, M 30 ± 17), 28% ($n = 78$) were under 16 years of age. The diagnosis was established by kidney biopsy in 89% and rectal biopsy in 11% of the cases. The number of patients with ESRD was 131 (38%), and these were all currently on renal replacement therapy.

The aetiological distribution of the 287 cases is shown in Table 1. Familial Mediterranean fever (FMF) and tuberculosis were the two major causes of amyloidosis, being followed by bronchiectasis [with or without chronic obstructive lung disease (COLD)], rheumatoid arthritis (RA), spondylarthropathy (SpA) and chronic osteomyelitis.

The most frequent presenting sign was oedema accompanied by proteinuria in 88% of the cases (Table 2). Hepatomegaly or splenomegaly were reported in 17 and 11% of the cases respectively. The mean systolic and diastolic blood pressures were respectively 115 ± 26 and 73 ± 15 mmHg, and 12% of the cases were hypertensive. A family history of amyloidosis was present in 16% ($n = 47$) of the cases and 73% ($n = 220$) of the cases were on colchicine treatment.

Table 1. Aetiological distribution of secondary amyloidosis in Turkey

Aetiology	*n*	%
FMF	183	64
Tuberculosis	28	10
Bronchiectasis and COLD	18	6
Rheumatoid arthritis	12	4
SpA	10	3
Chronic osteomyelitis	7	2
Others[a]	14	4
Unknown	21	7
Total	287	100

[a]Behçet's disease (4), Castleman disease (3), Still's disease (1), valvular heart disease (1). COLD, chronic obstructive lung disease.

Table 2. Clinical findings at presentation

Clinical findings	*n*	%
Oedema	260	88
Hepatomegaly	48	17
Splenomegaly	33	11
SBP (mmHg)	115 + 26	–
DBP (mmHg)	73 + 15	–
Hypertension	35	12

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Discussion

This study was undertaken to obtain epidemiological information about secondary amyloidosis in Turkey with a special focus on aetiological distribution.

FMF appears to be the leading cause of AA amyloidosis in our country, followed by tuberculosis and bronchiectasis, with or without COLD. Chronic arthritis due to RA or seronegative SpA is the underlying disorder in only 8% of the cases of secondary amyloidosis in our series. These results are in accordance with previous reports from Turkey [3,4].

FMF is a hereditary disorder, transmitted as a recessive trait that affects mainly Jews, Armenians, Arabs, Druze, Assyrians and Turks [5,6]. There are, however, no published formal prevalence or incidence studies for FMF. In one of the major paediatric rheumatology clinics, however, the prevalence was reported to be 24% in 933 children registered at the clinic, and was second only to the prevalence of juvenile chronic arthritis [7]. It is also of note that tuberculosis ranks second as the aetiology of systemic amyloidosis. Although there are no well-documented prevalence or incidence figures for tuberculosis in Turkey, indirect evidence suggests that it is higher than supposed. A tuberculosis skin test was positive in 25% of a population that did not have prior vaccination against the disease [8]. The publicized incidence was 34.9/100 000 based on the data of cases reported to health authorities; this underestimates the true incidence, because a large number of patients are unreported [8]. Furthermore, both the prevalence and the incidence of multi-drug-resistant disease seem to be high in Turkey at 47% [9,10] for which the major reason appears to be non-compliant use of multiple medications.

It is widely accepted, and supported by clinical data, that regular and compliant use of colchicine not only decreases the frequency of acute attacks in FMF but also prevents the development of systemic amyloidosis in the long term [11]. We and others have reported the regression of amyloid deposits in renal amyloidosis secondary to FMF following regular colchicine treatment [12,13]. Although the role of colchicine in other

forms of secondary amyloidosis has not been well established [14,15], the high consumption of colchicine in Turkey suggests that it is also used in secondary amyloidosis caused by diseases other than FMF. Further studies are needed to confirm the suspicion that colchicine may also be effective in secondary amyloidosis other than that due to FMF.

Most information on the epidemiology of amyloidosis is derived from autopsy data. In several large series, the prevalence of AA amyloidosis varied from 0.50 to 0.86% [2,16]. Dilsen *et al*. [17] reported 106 patients with histologically proven secondary amyloidosis among 2340 cases of rheumatic diseases, with a calculated prevalence of 4.53%. Lofberg *et al*. [18] reported finding 19 cases of renal amyloidosis in 1158 consecutive autopsies, 10 of which were secondary amyloidosis. Six of the 10 cases had RA, the other four had systemic lupus erythematosus, pleural empyema, cholangitis with liver abscess and generalized atherosclerosis without any other underlying risk factor for AA amyloidosis. In a Dutch series, RA is the most frequent cause of AA amyloidosis [19], followed by recurrent pulmonary infection (11%), Crohn's disease (5%), ankylosing spondylitis (5%), tuberculosis (3%), osteomyelitis (2%), FMF (2%) and Hodgkin's disease (2%). No (idiopathic) aetiological factor had been detected in 5%. Evidence suggests that RA has a milder course in developing countries including Turkey, which might account for the paucity of RA among the aetiology of AA amyloidosis in our series [20,21].

It is widely accepted that amyloidosis coexists with hypotension. However, Hazensberg and Rijswijk [19] suggest that moderate hypertension occurs in 20–35% of patients with amyloid nephropathy. In our series, the mean systolic and diastolic blood pressures were mostly in the lower range, and hypertension was present in 12% of the cases.

We specifically asked for a family history of amyloidosis. Recent evidence suggests a genetic susceptibility to the development of amyloidosis in the face of a concomitant chronic inflammatory condition [22]. In our series, 16% of the cases had a family history of amyloidosis, all accompanying FMF.

The high number of patients with ESRD in our cohort may indicate a bias, since all of them were from nephrology clinics. Nevertheless, development of ESRD is the most serious complication of secondary amyloidosis.

In conclusion, FMF is the leading cause of renal amyloidosis in Turkey, followed by tuberculosis. The early diagnosis and treatment of both diseases may prevent this serious complication, which in turn leads to ESRD.

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Received for publication: 14.11.01
Accepted in revised form: 4.7.02