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Renal involvement in amyloidosis. Clinical outcomes, evolution and survival

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SUMMARY

Background: *Systemic amyloidosis is a disease resulting from extracellular deposition of fibrillar protein in various organs. Main systemic amyloidosis are: primary (AL) and Secondary (AA). The kidney is usually involved, conferring and adverse prognosis. In the last decade there has been a change in the aetiology of AA amyloidosis.*

Objectives: *To analyse the incidence of AL and AA amyloidosis in our current population as well as the aetiology of AA amyloidosis. To describe clinical outcomes, renal involvement and survival.*

Patients and methods: *We performed a descriptive analysis of all cases of amyloidosis diagnosed from 1992 to 2004 in our hospital. Diagnosis was assessed on histological criteria: positivity Congo Red stain. Clinical data, renal involvement, dialysis treatment and survival were analysed.*

Results: *76 cases, 44 women, mean age 70.7 ± 12. Types: 55 AA (72%), 21 AL (28%) systemic amyloidosis. AA aetiology was: 66% rheumatic disorders, 28% infectious disease, 6% others. Incidence for AL was 4.6 and for AA 12.2 cases/million. Renal involvement was present in 75% at diagnosis (69% Creatinine clearance < 60 ml/min, 37% urinary protein > 3 g/24 hours). 21 cases (28%) progressed to renal disease stage V in the 8.1 ± 9.8 months follow up period, and 14 cases started dialysis treatment (10 HD, 4 CAPD). In 7 cases (33%) dialysis was not indicated due to their poor clinical condition, short life expectancy and bad quality of life. Mean global survival at diagnosis was 55% and 40% at 12 and 24 months (AL 58% and 19%; AA 55% and 44%). Mean survival from the start of dialysis was 30% and 5% at 12 and 24 months.*

Conclusions: *Although amyloidosis has a low incidence in our population, the kidney is usually involved. Rheumatological disorders are the principal aetiology of AA amyloidosis. Long term survival is poor, specially for AL.*

Key words: ***Amyloidosis, renal failure, dialysis, survival.***

AFECTACIÓN RENAL EN LA AMILOIDOSIS. CARACTERÍSTICAS CLÍNICAS, EVOLUCIÓN Y SUPERVIVENCIA

RESUMEN

Fundamento: *La amiloidosis es una enfermedad sistémica caracterizada por el depósito extracelular de material proteico fibrilar en disposición en lámina beta plegada. Las principales formas de amiloidosis sistémicas son la amiloidosis primaria (AL) y la secundaria (AA). La afectación renal es frecuente, confiriéndole un pronóstico poco favorable. En los últimos años estamos asistiendo a un cambio en la etiología de las formas secundarias.*

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Objetivo: *Analizar la incidencia de AL y AA en nuestra área de referencia así como la etiología de AA. Describir la presentación clínica, la afectación renal y la evolución.*

Material y métodos: *Análisis descriptivo de los casos de amiloidosis de nuestro hospital en el período 1992-2004. Criterio diagnóstico: histología positiva para Rojo Congo. Se analizan las variables clínicas, afectación renal, inclusión en diálisis y supervivencia.*

Resultados: *Setenta y seis casos, 44 mujeres, edad media 70,7 ± 12. Tipos: 55 AA (72%), 21 AL (28%), etiología AA: 66% reumatológicas, 28% infecciosas, 6% otras. La incidencia fue: AL 4,6 y AA 12,2 casos /millón. El 75% tenían afectación renal al diagnóstico (69% ClCreat < 60ml/min, 37% proteinuria > 3 g/24 horas). 21 casos (28%) evolucionaron a insuficiencia renal grado V en un tiempo medio de 8,1 ± 9,8 meses, iniciando diálisis 14 pacientes (10 HD, 4 CAPD). En 7 casos (33%) no recibieron tratamiento dialítico por la importante afectación del estado general y la mala calidad de vida. La supervivencia actuarial global desde el momento del diagnóstico fue de 55% y 40% a los 12 y 24 meses (AL 58% y 19%; AA 55% y 44%). La supervivencia actuarial desde el inicio de diálisis fue de 30% y 5% a los 12 y 24 meses.*

Conclusiones: *Aunque la amiloidosis es una patología con escasa incidencia en la población general, la afectación renal es muy frecuente. Las enfermedades reumatológicas son la principal causa de AA. La supervivencia es limitada, especialmente para las formas AL.*

Palabras clave: ***Amiloidosis. Insuficiencia renal. Diálisis. Supervivencia.***

INTRODUCTION

Amyloidosis is the term that defines a group of diseases characterized by extracellular deposition of proteinic fibrillar material in a beta-sheet disposition. Amyloidal substance has high affinity for Congo red stain and characteristically presents apple-green birefringence on polarized light. The several amyloidosis subtypes are classified by their localized or systemic distribution, besides familial and senile types and those hemodialysis-related. The main types of systemic amyloidosis are primary amyloidosis (AL) and secondary amyloidosis (AA).[1] The terminology used for amyloidosis disease classification includes two letters: the first one is an «A» for amyloid and the second one refers to the specific fibrillar protein. In AL amyloidosis, the fibrillar protein is made up essentially of immunoglobulin light chain protein, and may be an isolated form or related with multiple myeloma. AA amyloidosis is made up of fibrillar protein A, which derives from a liver synthesis plasma precursor that is an acute phase reactant that increases with inflammatory stimuli associated with chronic infectious and inflammatory diseases.

Studies published in the 1980's pointed out chronic diseases as the main etiology of amyloidosis.[2,3] Still having a relevant role, in recent times we have witnessed an important change in the disease etiology, today being rheumatic diseases the main cause of AA amyloidosis.[4,5]

Systemic amyloidosis presents in a variety of sings and symptoms, the kidney being a frequently involved organ, thus conferring a poorly favorable prognosis. Although it may be a scantly relevant pathology, it should always be considered in the differential diagnosis of the causes of progressive renal failure with or without proteinuria.

We describe the cases of systemic amyloidosis (AL and AA) diagnosed at our Center with the aim of analyzing the incidence of AL and AA in the general population from our reference area, as well as the features and course of renal involvement.

MATERIAL AND METHODS

We performed a descriptive analysis of all patients diagnosed with amyloidosis at our Hospital in the period comprised between January of 1992 and

March of 2004. This is a general hospital with a population reference area of 380,000 inhabitants.

The study group was obtained from the pathology laboratory database with a diagnosis of amyloidosis. Not included in the study were localized and senile subtypes of amyloidosis and those due to dialysis-associated b-2 microglobulin deposition. The diagnosis was done after in depth study of samples obtained from different tissues (abdominal subcutaneous fat, kidney, rectum, liver, skin, lymph node, and bone marrow aspirate) and sent to the pathology laboratory. The diagnosis of amyloidosis was based on the demonstration of the typical features of amyloid substance: positive Congo red stain and birefringence with polarized light. The criteria used for AA forms were the presence of associated chronic disease, sensitivity to potassium permanganate and immunohistochemistry in available cases. AL forms were diagnosed if there was resistance to potassium permanganate, positive immunohistochemistry for AL, and the presence of a monoclonal spike in the blood or urine.

Vital statistics, symptoms and sings at the time of diagnosis, and the presence of systemic disease, either inflammatory or infectious, were gathered from the reviewed clinical charts. Renal and liver function biochemical parameters, nutritional parameters, and hematological variables were analyzed from laboratory data. Renal failure was considered when creatinine clearance, calculated or estimated through the simplified MDRD formula, was < 60 mL/min, and nephrotic proteinuria when > 3 g/day.

Renal disease progression, type of treatment for renal failure (conservative or replacement), and actuarial survival were analyzed, both at the time of disease diagnosis and at the onset of dialysis program.

Results are expressed as mean ± standard deviation. The actuarial survival analysis was done by the Kaplan-Meier method.

RESULTS

Within the 12 years analyzed (1992-2004), 76 patients were diagnosed with systemic amiloidosis in our Center (44 women and 32 men), with a mean age of 70.7 ± 12 years. Fifty-five (72%) were AA amyloidosis and 21 (28%) AL amyloidosis.

Considering our reference population, the incidence of amyloidosis was 12.2 and 4.6 cases/pmp/year for AA and AL, respectively. As for amyloidosis etiology, 36 (66%) were of rheumatic origin, 16 (28%) of infectious origin, and 3 (6%) associated to other pathologies. Table I shows the different conditions that account for amyloidosis. Among rheumatic causes, we highlight the preponderance of rheumatoid arthritis with 26 cases. As for infectious causes, the main condition was respiratory pathology presenting as bronchiectasia, with 9 cases.

In 31 (40%) patients, diagnosis was done through abdominal subcutaneous tissue biopsy (ASTB), in 21 (27%) by renal biopsy, in 14 (18%) by rectal biopsy, in 5 (7%) by liver biopsy, and in 5 cases by biopsy of other tissues (2 subcutaneous, 2 lymph node, and 1 bone marrow aspirate). During the follow-up, in 9 patients histological material was obtained from other sites within the study of intercurrent conditions confirming the amyloid deposition. In renal biopsy material, amyloidal deposits were mainly located at a glomerular level as mesangial nodules. In 60% of the cases, amyloid deposition could be seen at the extraglomerular vessels.

A total of 47 ASFB were done, the result being negative in 16cases, the diagnosis being confirmed by biopsies obtained from other tissues. These results represent a 65% (31/47) sensitivity with the ASFB technique.

The main clinical manifestations motivating clinical consultation and leading to amyloidosis diagnosis were: edema (44%), fatigue (21%), and diarrhea (22%). As for laboratory data regarding renal function at the time of diagnosis we sort out: urea 78 ± 60 mg/dL, creatinine 1.8 ± 1.4 mg/dL. Mean proteinuria in 24-h urine samples was 4.1 ± 5.8 g.

Table I. Main etiologies associated with AA amyloidosis

Etiology	Cases (%)
Rheumatic	**36 (66%)**
Rheumatoid Arthritis	26
Rheumatic Polymyalgia	4
Ankylosing Spondylitis	2
Generalized Psoriasis	1
Cutaneous Vasculitis	1
Polyarthritis	1
Infectious	**16 (28%)**
Bronchiectasia	9
Chronic Ostomyelitis	2
Repeated urinary infections	2
Tuberculosis	1
Xanthogranulomatous Pyelonephritis	1
Cellulitis	1
Others	**3 (6%)**
Crohn's disease	1
Paraneoplasic (Colorectal)	1
Unknown	1

Table II shows biochemical and hematological parameters as a whole and by type of amyloidosis. Only ESR (AA 84.2 and AL 54.9 mm at the 1st hour) showed significant differences between both groups.

According to K/DOQI-NFK guidelines of stage classification of renal disease , 37% of the patients were in stage III, 25% in stage IV, and 7% in stage V, at the time of diagnosis. With a mean follow-up time of 8.1 ± 9.8 months, 33 (43%) patients progressed to stage V, 21 of them requiring renal replacement therapy. In seven (33%) patients, it was decided not to initiate a dialysis program and proceed with only conservative measures due to severe general condition and poor quality of life. This decision was adopted with patient's agreement if he/she was able of expressing his/her opinion or, by default, jointly between the medical caring team and the patient's closest relatives. Among the 14 remaining cases, 10 chose to enter into a hemodialysis program, and 4 into peritoneal dialysis. Throughout the study, 470 patients started on hemodialysis in our Unit, amyloidosis representing 3% of the causes of dialysis therapy onset in our Center.

Throughout the study 51 (67%) patients in total died, with a mean follow-up period of 19.7 ± 26.5months. The main mortality causes were: 15 (29%) infectious, 11 (22%) cardiovascular, 3 (6%) heart failure, 7 (14%) end-stage (stage V) renal failure without having started on dialysis, 7 (14%) unknown, and 8 (16%) died from other causes. The whole actuarial survival for the disease at 6, 12, and 24 months from diagnosis was 63%, 55%, and 40%, respectively.

Figure 1 shows the actuarial survival curve by type of amyloidosis. We observe that survival at 6, 12, and 24 months was 62%, 55% and 44% for AA amyloidosis, respectively, and 64%, 58% and 19% for AL amyloidosis, respectively. Survival once dialysis program had been initiated was 11.61 ± 16.7months, and actuarial survival at 6, 12, and 24 months was 46%, 30% and 5%, respectively.

Table II. Main analytical data for the whole group and separately by type of amyloidosis

	Global n = 76)	Primary (n = 21)	Secondary (n = 55)
ESR (mm 1st h)	74.7	54.9	84.2 (p < 0.03)
CRP (mg/dL)	4.8	2.4	5.8
Hemoglobin (g/L)	16.6	14.7	13.8
Hematocrit	36.6	38.8	35.7
Urea (mg/dL)	78.3	64.8	84.8
Creatinine (mg/dL)	1.8	1.5	1.9
Albumin (g/dL)	26.9	26.5	26.6
Proteinuria (g/24 h)	4.1	3.8	4.32

DISCUSSION

Amyloidosis represents an uncommon condition, although it entails high repercussion on patient's quality of life and considerable morbimortality. When analyzing the data from autopsy series, the incidence of systemic amyloidosis lays between 0.5-0.86%, with important variability depending on the studied geographical area.[6,7] A study published by Cazalets et al.[8] analyses the demographical data of 43 cases of systemic amyloidosis followed for 5 years in France, establishing an incidence of 8.6 cases-pmp/year, with a mean age at diagnosis of 63.7 years. In our study, patients had a mean age of 70.7 years at the time of diagnosis, with a clear-cut preponderance of female gender for AA amyloidosis (61% female vs. 39% male) and a high incidence of secondary amyloidosis over the primary forms of the disease (63% AA vs. 245% AL). These data are in agreement with most of the studies, although mean age and incidence in our study are slightly higher. Progressive aging of the population, as well as the increase in numbers of rheumatic conditions mainly woman-related, might explain the outcomes found in this study.

In the series published early on, chronic infections represented the main etiology of AA amyloidosis, although little by little rheumatic diseases have taken up a more important role.[2-5] In the present study, the main etiology for AA amyloidosis is comprised by rheumatic disease, rheumatoid arthritis being the most frequent, and infectious pathologies ranking second. These changes regarding etiology might be explained by a higher life ex-

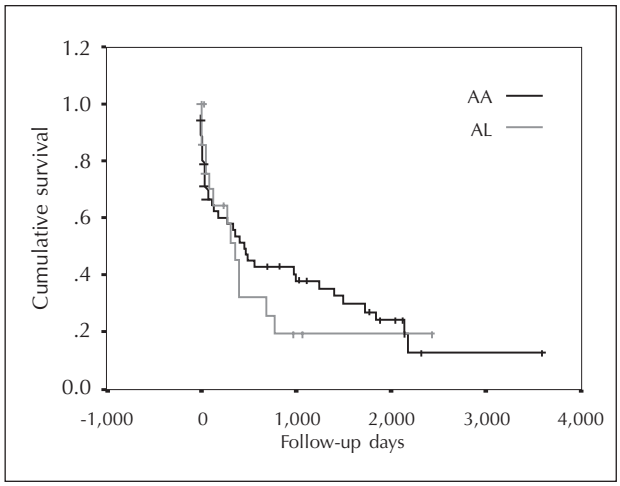

Fig. 1.—Actuarial survival curve by type of amyloidosis (AA and AL) from time of diagnosis.

pectancy of patients with chronic inflammatory conditions as well as an improvement of therapy of infectious processes.

Among the several organ and tissues affected by amyloidosis, the kidney is the most frequent one (80-90%), conferring a poor prognosis and high morbidity along the progression of the disease.[9,10,11] This renal involvement is mainly manifested as proteinuria, generally within the nephrotic range, and renal failure. Amyloid substance deposits are frequently severe at a glomerular level. Occasionally, these deposits are of vascular preponderance and lead to a more rapid progression of renal failure. Exceptionally, amyloid substance deposits involve tubular structures presenting with the typical manifestations of these syndromes.

The presence of other symptoms such as fatigue, joint and muscular pain, ascites, or diarrhea (a main symptom described in gastrointestinal involvement)[12] would be attributable to amyloid deposition in the heart, joints and bones, liver, or gut, evidencing the «systemic» nature of this condition. In general, we did not observe differences by clinical manifestations, symptomatology, or presenting forms depending on the amyloid type in our study.

One of the main problems that the clinician faces before amyloidosis suspicion is histological confirmation.[13,14] The choice of the study tissue is difficult since all organs are not involved with the same degree, frequency and promptness, keeping in mind that biopsy is a technique associated with complications. The yield of both kidney and liver biopsy is very high, being higher than 95% in several published studies,[4,5] but the high rate of hemorrhagic complications in these patients together with the need for hospitalization for the procedure make this method somehow limited for diagnosis. Deep rectal biopsy that includes the submucosa, where mainly the amyloidal substance deposits, shows up as a high yield diagnostic technique (greater than 90%). Its sensitivity and low complication rate make of it the first choice diagnostic procedure in many centers.[15]

Some authors have suggested that subcutaneous abdominal fat biopsy is a simple procedure with no complications and with an estimated sensitivity of 57-75%, according to several authors.[16,17] In our study, the sensitivity was 65%. Although the results are average, its innocuousness and easy performance make it a useful tool as an initial assessment technique. In case of being negative, and if disease suspicion remains high, it may histologically confirmed by another technique, considering in the first place performing deep rectal biopsy.

The fact that 33% of the patients needing renal replacement therapy did not started on dialysis program, due to severe general status and poor quality of life, deserves a special comment. The short follow-up period until emergence of ESCRF also stands out, highlighting the late diagnosis of this condition in most of the cases, when there already exists a wide systemic involvement and the disease is in very advanced stages.

The prognosis of patients with amyloidosis is very poor, and their mortality is especially high when there is kidney or heart involvement,[4,18,19] infectious conditions and cardiovascular pathology being the main mortality causes.[2-5,20]

In this sense, the work by Martinez Vea et al.[21] shows a survival rate of 72%, 62%, and 44% at one, two, and six years when analyzing 48 patients on dialysis with systemic amyloidosis and mean age of 52 ± 2.1 years. In a study by Moroni et al.[22], which comprised 48 Italian patients on dialysis with mean age of 53 ± 14 years and amyloidosis, one-year and five-year survival was 68% and 30%, respectively, with no differences shown by type of dialysis chosen. Recently, Torregrosa et al.[5] published survival rates of 68% at 6 months and 43% at one year from starting on dialysis in a series of 31 patients with renal amyloidosis. The results from our series are slightly lower, with a survival rate at 6, 12, and 24 months for patients starting on a dialysis program of 69%, 30% and 5%, respectively. These differences may be explained by two factors: in the first place, the older age of our patients (73 ± 2.8 years); and secondly, a change of inclusion criteria into dialysis programs, currently less restrictive, so that patients that would not have previously been included into a dialysis program because of their co-morbidity are currently admitted.

It has been suggested that the prognosis of AA amyloidosis tends to be better than that of AL forms; however, other authors have not shown any difference.[2-4,23,24] In the present series, AL amyloidosis shows a more aggressive course and lower survival from 24 months of follow-up and on (44% AA, 19% AL).

In summary, systemic amyloidosis is a low-incidence pathology in our reference area, where rheumatic diseases account for the main cause of AA amyloidosis, frequently having renal involvement. In spite of its low incidence, it accounts for a non negligible cause of entrance into dialysis, with a poor prognosis and high morbimortality. A third of patients have not been included into dialysis programs due to their severe general status and low quality of life.

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