AL amyloidosis in the Chilean public health system: a pending debt. Multicenter study of the Chilean Monoclonal Gammopathies Cooperative Group

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ABSTRACT

Background: Immunoglobulin light chain (AL) amyloidosis is a rare and underdiagnosed entity. **Aim:** *To characterize patients with AL amyloidosis in Chilean public health centers.* **Material and Methods:** *We conducted a retrospective, multicenter study. Public centers of the Chilean Monoclonal Gammopathies Cooperative Group were asked to search for patients with AL amyloidosis in their databases. Epidemiological, clinical and laboratory characteristics were evaluated.* **Results:** *Forty-two patients aged 22 to 84 years were found. Twenty four percent had localized AL amyloidosis; 64% had a lambda light chain clone; 47% were associated with multiple myeloma and 9% with non-Hodgkin lymphoma. The most commonly involved organ was the kidney (76%). Serum free light chains were measured in 31% and an echocardiogram was performed in 74% of patients. Seventeen percent of patients received only palliative care, 17% were treated with bortezomib, 21% with thalidomide, and 40% with melphalan. No patient was transplanted. The mean overall survival (OS) of the group was 19 months. The 5-year OS was 28%.* **Conclusions:** *It is important to obtain these realistic, national data to initiate strategies to improve early diagnosis and proper management of this disease.*
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Key words: *Amyloidosis; Bortezomib; Multiple Myeloma; Paraproteinemias; Transplantation.*

Amiloidosis AL en el sistema público de Chile: una deuda pendiente. Estudio multicéntrico

La amiloidosis AL es una entidad poco frecuente y subdiagnosticada. Mientras todo el mundo discute sobre las nuevas herramientas diagnósticas y terapéuticas, en Chile y en América Latina en general, estamos lejos de esa realidad. El objetivo del presente estudio fue caracterizar a los pacientes con amiloidosis AL en centros del sistema público de nuestro país. Se realizó un estudio retros-

pectivo, multicéntrico, descriptivo. Los centros públicos del grupo cooperativo hematológico chileno buscaron en sus bases de datos pacientes diagnosticados con amiloidosis AL. Se evaluaron las características epidemiológicas, clínicas y de laboratorio. La edad media fue de 65 años. A 24% de los pacientes se les diagnosticó amiloidosis AL localizada; 64% tuvo paraproteína con cadena ligera lambda; 47% se asoció con mieloma múltiple y 9% con linfoma no Hodgkin. El órgano afectado con mayor frecuencia fue el riñón (76%). Las cadenas ligeras libres de suero se realizaron en 31% y ecocardiograma en 74%. El 17% recibió solo cuidados paliativos, 17% recibió tratamiento con bortezomib, 21% con talidomida y 40% con melfalán. Ningún paciente fue trasplantado. La media de sobrevida global (SG) del grupo fue de 19 meses. La SG a 5 años fue de 28%. Es importante reportar estos resultados nacionales para iniciar estrategias que mejoren tanto el diagnóstico temprano como el tratamiento de esta patología. Por lo tanto, mejorar la sospecha diagnóstica es crucial.

Palabras clave: *Amiloidosis; Mieloma Múltiple; Trasplante Autólogo; Talidomida; Bortezomib; Gammapatía Monoclonal.*

AL amyloidosis is a rare and underdiagnosed entity, where pathogenic monoclonal light chains are produced by a small clone of plasma cells or, rarely, by a mature B cell clone[1,2]. These pathogenic proteins undergo a conformational change which renders them insoluble, favoring their deposition in tissues and eventually organ malfunction[3,4]. Amyloidosis has an estimated incidence of 3-14/1 million inhabitants/year, depending on the geographical area[5,6].

While the whole world discusses about the new diagnostic and therapeutic tools, in Chile, and Latin America in general, we are far from that reality.

There is little information about AL amyloidosis in Chile, consisting mainly on case reports[7,8]. The largest report was in 2005, where 11 cases were described[9].

The aim of the present study is to characterize patients with AL amyloidosis in public health centers throughout the country.

Materials and Methods

We conducted a retrospective, descriptive, multicenter study. Cases were collected between 2010 and 2018.

The public centers are members of the Chilean Monoclonal Gammopathies Cooperative Group, they were asked to search in their databases to look for patients diagnosed with AL amyloidosis.

In all centers, the diagnosis of AL amyloidosis was made with a positive Congo red stain on tissue biopsy. Affected organs were determined by biopsy or according to the definition of Gertz et al[10]. Epidemiological, clinical and laboratory characteristics were evaluated.

A descriptive statistical analysis was done. Overall survival (OS) was calculated with Kaplan Meier curves and a comparison was made with log Rank test.

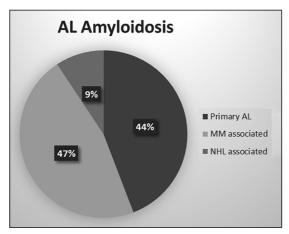The present study was approved by the corresponding Ethics Committee.

Results

Data was collected from 42 patients of eight public health centers.

The main characteristics are detailed on Table 1. The median age was 65 years, ranging from 22 to 84 years. The male to female ratio was 1: 0.75. Twenty four percent were diagnosed as localized AL amyloidosis; paraprotein was found in all the patients, and 64% presented with a lambda light chain clone; 47% of cases were associated with multiple myeloma (MM), and 9% with non-Hodgkin lymphoma (NHL) (Figure 1), 2 MALT lymphomas, 1 lymphoplasmacytic lymphoma, and a non-characterized low grade B cell lymphoma. The most frequently involved organ was

Table 1. Patient's characteristics and analysis by group: primary AL amyloidosis, MM-associated AL amyloidosis and NHL-associated AL amyloidosis (p < 0,5)

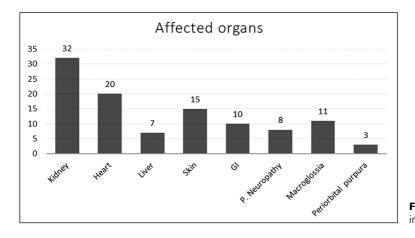|	Total (n = 42)	Primary amyloidosis (n = 18)	MM-associated (n = 20)	NHL-associated (n = 4)	p value
Male, n (%)	24 (47)	11 (61)	12 (60)	1 (25)	NS
Median age, years (range)	65 (22-84)	58 (33-84)	65 (22-77)	63 (56-77)	NS
iFLC= Lambda, n (%)	27 (64)	12 (67)	13 (65)	2 (50)	NS
iFLC= Kappa, n (%)	13 (31)	5 (28)	7 (35)	1 (25)	NS
Heavy chain only, n (%)	2 (5)	1 (5)	0 (0)	1 (25)	NS
Localized involvement, n (%)	10 (24)	5 (28)	3 (15)	2 (50)	NS
Multi-organ involvement, n (%)	32 (76)	13 (72)	17 (85)	2 (50)	NS
Cardiac involvement, n (%)	20 (48)	10 (56)	10 (50)	0 (0)	NS
Renal involvement, n (%)	32 (76)	14 (78)	17 (85)	1 (25)	NS

NS: not significant.

Figure 1. Frequency of primary AL amyloidosis and associated AL amyloidosis.

the kidney (76%), followed by the heart (48%) (Figure 2). The analysis by group: 1.- Primary amyloidosis, 2.- MM-associated amyloidosis, and 3.-NHL-associated AL amyloidosis showed no statistical difference between them (Table 1).
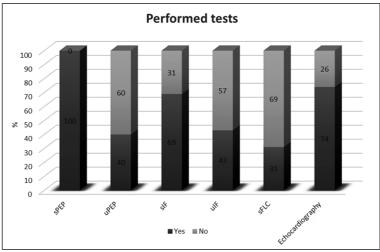
Regarding diagnostic tests (Figure 3), 100% reported having performed serum protein electrophoresis (sPEP), 69% serum immunofixation (sIFE) and 43% urine IFE. Serum free light chains (sFLC) were performed in 31% of the patients.

Heart involvement by echocardiogram was looked for in 74%, and renal involvement was screened in 98%.

As seen in Table 2, the most frequently performed biopsies were bone marrow (52%) and

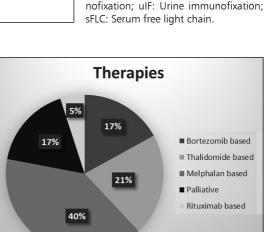**Figure 2.** Frequency of affected organs in the studied patients.

Figure 3. Diagnostic tests. Performed test are shown in dark gray. sPEP: Serum protein electrophoresis; uPEP: Urine protein electrophoresis; sIF: Serum immunofixation; uIF: Urine immunofixation; sFLC: Serum free light chain.

Table 2. Most frequent performed biopsies and frequency of positive diagnosis

Biopsy Site	Performed n (%)	Diagnostic n (%)
Bone marrow	22 (52%)	10 (45%)
Subcutaneous fat	16 (38%)	7 (44%)
Kidney	14 (33%)	14 (100%)
Gastrointestinal	11 (26%)	6 (55%)

Figure 4. Frequency of different therapies in the studied patients.

subcutaneous fat tissue (38%), being these samples diagnostic in 45% and 44% of cases, respectively. Renal biopsy was performed in 33% of the cases, with a positive diagnosis in all of them.

Treatment was heterogeneous: 17% were treated with bortezomib based therapy, 21% with cyclophosphamide, thalidomide, and dexamethasone (CTD), 40% with melphalan based therapy, and 17% received only palliative care. No patient received a bone marrow transplant.

The median OS of the group was 19 months. The 3-year OS was 38%, and the 5-year OS 28% (Figure 5). There was no survival difference between patients with or without associated MM (5-yr OS of 22% vs 24%; p = 0.8), with or without use of novel agents (5-yr OS of 15% vs 38%; p = 0,09), localized versus systemic amyloidosis (5-yr OS of 36% vs 27%; p = 0,6) or with or without cardiac involvement (5-yr OS of 25% vs 31%; p = 0.31).
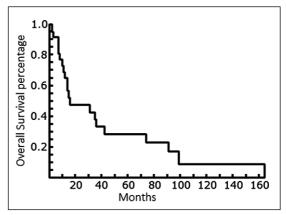

Figure 5. Cohort Overall survival (OS). The median OS was 19 months.

Discussion

This is to our knowledge, the larger experience published in Chile and Latin-America on this topic.

The scarce number of patients may be due to registry deficiency in our healthcare system. This is further favored by lack of clinical suspicion and reduced access to diagnostic tools.

Epidemiological and clinical characteristics

The demographic and clinical characteristics proved to be similar to what is reported in the international literature. The disease is more frequent in men, and the median age is approximately 65 years, according to series carried out in America, Europe and Asia[11-13].

Half of our patients were MM-associated, when the described rate is between 10-15%. This may be attributed to the fact that the MM-amyloidosis association is well known by general physicians, and therefore, more often suspected and diagnosed.

In 5% to 7% of patients, AL amyloidosis is associated with an underlying IgM secreting lymphoma, usually lymphoplasmacytic and MALT type[14]. In our cohort we found 10%. Compared with patients who have non-IgM AL amyloidosis, these patients are described to be older, having a higher prevalence of neuropathy and lymph node involvement, and a lower proportion of cardiac involvement. This was not demonstrated in this study, most likely due to the low number of recruited patients.

Twenty four percent of patients were catalogued as localized AL amyloidosis. Much more than described in literature. The lack of complete organ involvement study might explain this result.

The most frequent light chain reported is lambda, in about 80% of patients. Our cohort was not the exception, although it was observed in only 64% of the patients. One explanation could be the high percentage of MM-associated AL amyloidosis in our cohort.

The most affected organs were the kidney, followed by the heart, which coincides with other series[11-13]. The results obtained regarding affected organs must be analyzed with caution, since not all the patients had a complete organ study. For example, 26% of patients did not have an echocardiogram performed, despite cardiac involvement is the most frequently reported.

As described, the most characteristic signs such as macroglossia and periorbital purpura were found in a small number of patients (26% and 7%, respectively).

Screening

Appropriate screening should include sIFE[15], urine IFE[16], and sFLC assay[17]. In a recent survey conducted by our group, it was observed that only a small percentage of public health centers have these three studies available (not published). This is a serious concern and partially explains the underdiagnoses of this disease in our country.

Diagnosis

For an accurate diagnosis, the standard recommendation is to perform a biopsy/aspiration of subcutaneous fat and a bone marrow (BM) biopsy[18,19], which would have a sensitivity of 85%[1,20]. This was not consistent with the results of our study, where the sensitivity of subcutaneous fat and BM biopsies was low, confirming the diagnosis in less than half of the cases. Larger studies are required to verify this low sensitivity of the standard anatomopathological recommended studies. Experienced pathologists are important for an accurate diagnosis, and it is a factor to take into consideration when analyzing the results of this study.

In the majority of cases, the diagnosis of AL amyloidosis was made only after biopsy of the affected organ was performed, which suggests a low level of suspicion of AL amyloidosis prior to the biopsy. Although biopsy of the affected organ increases sensitivity to 95%, being 100% in the case of renal biopsy in our cohort, this procedure should be indicated with caution due to its invasive nature.

Unequivocal amyloid typing using mass spectrometry in specialized laboratories is the basis for accurate diagnosis and subsequent treatment[22,23]. This technology is not available in Chile, where diagnosis relies on tissues testing positive to Congo red and immunohistochemical study. This also means that we cannot exclude other type of amyloidosis in our patients.

Prognosis

New biomarkers are currently being used for diagnosis, prognosis and follow-up. One of them

is the measure of sFLC[24]. In 2003, Palladini et al. described the sensitivity of NT-proBNP in diagnosis and prognosis for the first time[25].

The Mayo Clinic score is the main tool used to define prognosis[26,27]. In this score the NT-proBNP, troponin I and the difference of the involved light chain with the non-involved free light chain are included.

There is not enough data to evaluate prognosis in our studied patients, due to the lack of these markers in most of our centers.

Treatment

Unfortunately, the Chilean public health system has few treatment options. The current protocol continues being melphalan and dexamethasone, with no access to new drugs such as bortezomib. Although 17% of the patients were treated with bortezomib, the acquisition of this drug required cumbersome and time-consuming requests from each institution.

It is necessary to include bortezomib in our therapeutic arsenal as it is the drug that changed the vision of AL amyloidosis, demonstrating an excellent response of up to 71% complete response with cyclophosphamide- bortezomib- dexamethasone (CyBorD)[28,29]. Another effective treatment is BMDex (bortezomib, melphalan and dexamethasone), which has shown very good results, superior to CyBorD in patients with high tumor burden[30,31]. Moreover, a recent phase 3 study demonstrated a greater hematological and organ response with BMDex versus MDex[32]. This positive outcome may be due to a proven high sensitivity of the plasma cells to bortezomib[33].

There are new pharmacological treatments which are unattainable in our country at this time, which include studies with carlfilzomib, ixazomib, daratumumab and even anti-fibril antibodies[34-36].

Autologous stem cell transplantation

The introduction of autologous stem cell transplantation (ASCT) marked a major advance in the treatment of AL amyloidosis[37] as it has improved OS through the years with a 5-year OS up to 77% and a reduction in mortality at 30 and 100 days of 3% and 5%, respectively[38]. One study of 629 patients showed ~ 35% of patients obtaining complete remission and a median survival approaching up to 8 years[39]. Unfortunately, the bone marrow transplant program in the Chilean public health system is restricted, and amyloidosis is not currently an indication of it, which explains why no patient had bone marrow transplant in our registry. Furthermore, there is just one report in Chile of 6 AL amyloidosis patients with bone marrow transplant[40].

Survival

Survival has doubled worldwide in the last decade; 30 to 40% of patients are now surviving more than 10 years[12]. In Sweden, the median survival after diagnosis of AL amyloidosis is 3 years[41]. The results in Chile are far below this, with a median OS of less than 20 months, which requires further analysis of the situation. It seems that physicians often do not suspect this disease on time, leading to a delay in the diagnosis. It is also necessary to optimize and standardize the diagnostic tools in all public health centers where amyloidosis is treated. In addition, the therapeutic resources are currently also insufficient.

Continuous education regarding this pathology is peremptory, as the most important step to avoid underdiagnoses is the awareness of this disease[42]. An online survey from the Amyloid Research Consortium indicates that 37% of patients are not diagnosed until one year after the onset of initial symptoms, and an average of three medical appointments. Moreover, despite advances in therapeutic treatments, the frequency of sudden death within ≤ 90 days of diagnosis remains at 25% -30%[43]. Early detection can prevent cardiac damage and potentially reduce the risk of sudden death.

This study is limited by its retrospective nature, and small number of patients. In addition, data could not be obtained from all national public health centers nor was the requested data complete in all cases. Nevertheless, this is the reality in Chile and it is our belief that this initial report is necessary to generate a change.

Conclusion

There are shortfalls in the diagnostic study and treatment of AL amyloidosis in our public health centers. It is important to obtain realistic, national results to initiate strategies to improve both early diagnosis and management of this pathology. Improving awareness is therefore crucial.

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