Incidence and Natural History of Primary Systemic Amyloidosis in Olmsted County, Minnesota, 1950 Through 1989

By Robert A. Kyle, Athena Linos, C. Mary Beard, Reinhold P. Linke, Morie A. Gertz, W. Michael O'Fallon, and Leonard T. Kurland

No reports of the incidence rates for primary systemic amyloidosis (AL) have come to our attention. Records of all residents of Olmsted County, Minnesota, with a diagnosis of amyloidosis were obtained from the Mayo Clinic and its affiliated hospitals, as well as other medical groups that might have seen local patients for the period January 1, 1950 to December 31, 1989. Twenty-one patients fulfilled the criteria for the diagnosis of AL. The median age was 73.5 years, and 62% were men. In all but one patient the diagnosis was made ante mortem. The clinical data of the 21 patients were similar to those referral patients with AL seen at Mayo Clinic. Immunohistochemical stains were positive for monoclonal light chains in the amyloid deposits in 15 of the 21 cases. In six cases, tissue was not available for immunohistochemical studies. Three of the six patients without immunohistochemical stains had a free monoclonal \( \lambda \) light chain in the urine, and the other three had a monoclonal serum protein. Immunoelectrophoresis/immunofixation detected a monoclonal (M)-protein in the serum of 16 of 17 patients tested. A monoclonal light chain was found in the urine of 10 of 15 patients. The overall sex- and age-adjusted rate per million person-years was 6.1 from 1950 to 1969 and 10.5 from 1970 to 1989. The similarity of these rates suggests no significant increase over time.

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PRIMARY systemic amyloidosis (AL) is an uncommon disease that is characterized by the presence of amyloid fibrils, which are deposited mainly in the heart, kidney, gastrointestinal tract, peripheral and autonomic nerves, skin, joints, and blood vessels of virtually all organs. The amyloid fibrils consist of a fragment of an immunoglobulin light chain. The source of the light chains is a low-grade proliferative population of monoclonal plasma cells. The designation "AL" reflects the light chain origin of this type of amyloid.1,2

Mortality statistics for AL have not been reported in the United States, and we are unaware of any published studies of the incidence or prevalence of AL in the United States or other countries. The absence of epidemiologic data is indicative of the rarity of AL and the diagnostic difficulties in distinguishing AL from secondary amyloidosis (AA), familial amyloidosis (AF), and senile systemic amyloidosis (ASC).

During 1989, we saw 77 new patients with AL at the Mayo Clinic. They accounted for 9% of all patients who presented with a plasma cell proliferative process that year. This number of AL cases cannot be used for incidence estimates, because patients with a rare, serious disease who have a poor prognosis are likely to be referred to or to seek help at a tertiary medical center, particularly if that center is known to have a high level of interest in amyloidosis and if a prospective randomized study of treatment is in progress. Multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS) accounted for 14% and 66%, respectively, of the plasma cell dyscrasias seen at the Mayo Clinic in 1989.

It is difficult to estimate the incidence rates over time for AL because of changing criteria for diagnosis, changes in clinical practice, variations in methods of diagnostic indexing of medical records, and differing autopsy rates. However, a rare opportunity to minimize these limitations exists in Olmsted County, Minnesota, because medical care for the population of Rochester, MN and surrounding Olmsted County has been provided primarily by the Mayo Clinic and one other private group practice since early in this century. Virtually all medical, surgical, and pathologic diagnoses of significant illness among Olmsted County residents at any local health-care facility have been compiled in a centralized records-linkage system. Information in this central file is supplemented by a periodic search of the records of medical facilities in the surrounding counties where, on infrequent occasions, Olmsted County residents might have gone for medical care. Information from death certificates and autopsy reports for all county residents is also entered into the comprehensive diagnostic file for the defined population.

The relative stability of the local population (particularly in the elderly age groups, which are at higher risk for AL), the unusual centralization of high-quality medical care, the high rate of autopsy, and the centralized diagnostic indexing and records-linkage system used for many decades at the Mayo Clinic provide an exceptional source for studies of incidence rates and long-term trends in the population of Olmsted County. This report describes the incidence rates of AL and the trends over a 40-year period.

MATERIALS AND METHODS

The records of all Olmsted County residents with a diagnosis of amyloidosis, including primary, secondary, senile, localized, and familial amyloidosis, were obtained from the Mayo Clinic and its affiliated hospitals, the Olmsted Medical and Surgical Group, and

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the Olmsted Community Hospital for the period January 1, 1950 through December 31, 1989. To ensure that no cases of amyloidosis were overlooked, we obtained all death certificates or autopsy reports for Olmsted County residents with a diagnosis of amyloidosis and reviewed their medical records. A residency criterion was applied so that only those patients who had lived in Olmsted County for at least 1 year before the diagnosis of amyloidosis were considered to be residents. Any person known to have moved to Olmsted County to facilitate the diagnosis and treatment of symptoms of existing amyloidosis was excluded. All patients with amyloidosis from a secondary cause, those with a positive family history of amyloid, or those with amyloid localized to an organ were excluded.

The diagnosis of AL required the demonstration of amyloid in paraffin blocks from biopsy or autopsy tissue on the basis of apple-green birefringence when stained with alkaline Congo red and viewed under polarized light. The unlabeled immunoperoxidase method was used with antisera against purified amyloid fibril proteins, namely, Aα and Aλ light chains, AA (protein A), ATTR (prealbumin [transthyretin]), and AB (β2-microglobulin), and suitable controls to classify the type of amyloid in a double-blind fashion.

Fig 1. Cardiac amyloid deposits identified as Aα type by immunohistochemistry. (A) Section stained with Congo red; slightly darker areas indicate dye binding. Epicardia fatty tissue shows a broad subepicardiac band of amyloid, as well as amyloid in two arteries. (B) Adjacent section stained with anti-Aα (HAR). Note strong staining of all areas shown in (A). (C) All areas that bind Congo red and are immunohistochemically marked are strongly birefringent in polarized light. (Original magnification × 210.)
The incidence rate was estimated using decennial census data with appropriate extrapolations for intercensal years. The 95% confidence intervals were based on the rate ±2 SE. Survival was evaluated with the Kaplan-Meier method.

RESULTS

Twenty-one patients fulfilled the criteria for the diagnosis of AL. The median age was 75 years (range, 47 to 92 years). Thirteen patients were men and eight were women. There was no evidence of geographic clustering. No association with any occupation or education level was detected. All patients were white and mostly of Northern European or Hispanic.

Immunohistochemical staining of amyloid deposits in tissue section was performed in 15 cases: 11 (73%) were \(\lambda\) (Fig 1) and 4 were \(\kappa\). Tissue was not available for staining in the remaining six patients. Three of these six had a free monoclonal \(\lambda\) light chain in the urine, and the other three had a monoclonal serum protein.

Immunoelectrophoresis/immunofixation revealed a monoclonal (M)-protein in the serum of 16 of 17 patients tested (Table 1). Two additional patients (one in whom AL was diagnosed in 1957 and the other in 1965) had an M-spike in the serum protein electrophoretic pattern, but immunoelectrophoresis was not performed. One other had a normal serum protein electrophoretic pattern, and the remaining (21st) patient (in whom AL was diagnosed in 1952) did not have electrophoresis. The amount of the M-protein was modest—only two patients had a value of greater than 2.0 g/dL at diagnosis. Immunoelectrophoresis/immunofixation of the urine showed a monoclonal light chain in 10 of 15 cases (Table 1). Urine from three other patients had a normal electrophoretic pattern, and no urine studies were performed in the remaining three patients. An M-protein was not identified in the serum or urine from five patients. All five had tissues reactive with amyloid light chain antisera. Thus, the diagnosis of AL is certain.

The clinical data of the 21 Olmsted County patients were similar to those from our referral patients with AL. For example, among the Olmsted County patients, congestive heart failure was present in seven (33%), nephrotic syndrome in four (19%), macroglossia in four (19%), carpal tunnel syndrome in two (10%), hepatomegaly in two (10%), renal failure in two (10%), and orthostatic hypotension, intermittent claudication, cardiac arrhythmia, pseudo-obstruction of small bowel, and marked weight loss in one each. Rectal biopsy was positive in eight (67%) of 12 patients, and a bone marrow biopsy was positive for amyloid in five (42%) of 12 patients. Liver biopsy was positive in four, and carpal tunnel tissue, renal biopsy, small intestine biopsy, and abdominal fat aspirate accounted for the other positive biopsies.

Eighteen (86%) of the patients have died. The median duration of survival from diagnosis was 2.3 years (Kaplan-Meier method)\(^1\) (Fig 2). Twelve patients (60%) died of cardiac causes (congestive heart failure or arrhythmia), two died of an infection, and one died of intestinal obstruction. Three patients died of “amyloidosis,” but the terminal event was likely cardiac.

In all but one patient the diagnosis was made ante mortem. Approximately 15 other patients initially were thought to have AL, but were proven to have senile systemic amyloidosis on histochemical stains and thus they were excluded from this study. Thus, it is important to perform histochemical staining at autopsy in patients with systemic amyloidosis to confirm the diagnosis. This is the

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**Table 1. Serum and Urine M-Proteins on Immunoelectrophoresis/ immunofixation in 21 Patients With Amyloidosis in Olmsted County, Minnesota, 1950 Through 1989**

<table>
<thead>
<tr>
<th>Serum and Urine Proteins</th>
<th>Amyloid Tissue (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>IgG (\lambda)</td>
<td>8</td>
</tr>
<tr>
<td>IgG (\kappa)</td>
<td>3</td>
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</tr>
<tr>
<td>Not done*</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>21†</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>(\kappa)</td>
<td>2</td>
</tr>
<tr>
<td>(\lambda)</td>
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<td>Negative</td>
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</tr>
<tr>
<td>Not done</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
</tr>
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*Two patients had a serum M-spike on electrophoresis, but immunoelectrophoresis or immunofixation was not performed.
†Five of the 21 patients had no M-protein in the serum or urine.
only method that accurately distinguishes these amyloid syndromes.

The crude age- and sex-specific incidence rates for the total group are shown in Table 2. The overall age- and sex-adjusted annual rate per million person-years was 8.9. The age-adjusted rates were significantly greater in men (14.1) than women (5.7). The age- and sex-adjusted rates were 3.9, 7.6, 5.9, and 14.4 per million person-years for the four decades from 1950 through 1989 (Table 3). However, the wide confidence interval (CI) indicates that the trend toward increasing incidence rates with time (decades) was not statistically significant. The overall age- and sex-adjusted incidence rate was slightly higher for the most recent two decades (10.5; 95% CI, 5.2 to 15.9) than for the first two decades (6.1; 95% CI, 1.2 to 11.1) (Table 3). The wide CI is consistent with no significant increase over time.

Applying the rate of 8.9 per million to the US population of 250 million, assuming that there is no geographic variation, approximately 2,225 new cases of AL should occur each year.

**DISCUSSION**

AL is an uncommon disease, and no other population-based studies of AL have come to our attention. However, a few other sources may provide an approximation of frequency for comparison. AL was found in six (0.2%) of 3,414 autopsies conducted from 1937 to 1946 at the Royal Victoria Hospital in Belfast, Ireland, and in 43 (0.4%) of 11,586 autopsies performed at the same institution from 1961 to 1970. The increase probably reflects better recognition of AL in recent years, rather than an increase in incidence. van Rijsjwijk (personal communication, 1987) estimated the incidence of primary and secondary amyloidosis at one per 50,000 or 20 per million population. Two thirds of the cases were secondary amyloidosis, and the remainder were primary. Thus, the incidence of AL is approximately six to seven per 1,000,000 population.

The unique comprehensive medical data source available for the population of Olmsted County, Minnesota, has been of great value in determining incidence trends and prevalence rates for various diseases. We have published such data for several other rare diseases, including polycythemia vera, plasmocytoma, and polymyositis. These reports indicate that such measurements are possible, and they stimulate others to conduct surveys and provide rates for comparison so that a geographical and temporal pattern finally emerges.

The diagnosis of systemic amyloidosis requires the demonstration of amyloid in the biopsy specimen of an involved organ. This requires the clinical suspicion of amyloidosis and an appropriate biopsy. Furthermore, the type of systemic amyloidosis must be determined.

The diagnosis of AF is apparent when histologic proof of amyloid is found in a patient with the typical clinical features of AF and a positive family history. However, we have seen several patients without a family history of AF or other recognized hereditary disease, but in whom immunohistochemical staining detected the presence of amyloid deposits composed of transthyretin (prealbumin) and analysis of genomic cDNA confirmed a mutant transthyretin gene.

ASC1 is usually diagnosed at autopsy, but we have reported five patients with senile amyloidosis that was recognized ante mortem. These patients were recognized because immunohistochemical staining of the myocardium for transthyretin was performed. In our clinical experience, "nonsecretory" AL occurs in approximately 11% of patients with AL. The difficulty in interpreting studies that do not use immunohistochemical staining is that other forms of amyloidosis may be confused with AL.

The diagnosis of AL in our patients is certain. Sixteen of the 21 patients had a documented M-protein in the serum, and two others had a spike consistent with an M-protein. Immunohistochemical stains were positive for A<sub>α</sub> (three cases) or A<sub>λ</sub> (two cases) in the five patients without a demonstrable M-protein in serum or urine. Fifteen of the 21 patients had immunohistochemical staining that was positive for A<sub>α</sub> or A<sub>λ</sub> light chains; these results confirm the diagnosis of AL. Three patients without immunohistochemical staining had a free monoclonal λ light chain in the urine, and the other three had an M-protein in the serum. Thus, all 21 patients had either a monoclonal protein in the serum or urine or immunohis-
tochemical stains indicating amyloid of immunoglobulin light chain origin.

There was no case with a discrepancy between the clinical picture and the immunohistochemical result. The immunohistochemical investigation was performed in a double-blind fashion. The reagents used on tissue sections in this study are suitable for the classification of amyloid syndromes, according to our previous experience. The immunohistochemical diagnosis as established in this study is independent of the clinical features or other laboratory data. In contrast, anti-light chain antisera may fail to identify the correct amyloid class.

The sex distribution of the Olmsted County patients (62% men) was essentially the same as that in our referral patients with AL. The average age of Mayo Clinic referral patients is about 10 years younger than that of the local population. The older age of our local patients reflects the reluctance of elderly and frail patients or their physicians to arrange referral to a tertiary or distant medical center. It also indicates that local patients had available state-of-the-art invasive and other diagnostic techniques, as well as a greater suspicion for AL by the internists who attended them at Mayo Clinic. The median survival of 2.3 years in our 21 local patients is similar to the survival in our clinical referral practice.

Sera and urine are tested with immunoelectrophoresis and immunofixation to confirm the presence of a monoclonal light chain. Identification of a monoclonal light chain suggests the possibility of AL or multiple myeloma and related disorders. We also screen the urine of all patients with nephrotic syndrome for the presence of a monoclonal light chain. The association of nephrotic syndrome and a monoclonal light chain—especially if it is λ—is strong presumptive evidence of AL. The appropriate biopsies are then performed in these patients. These practices and a relatively high autopsy rate for the Olmsted County population may account for the increased case ascertainment in older residents of the county.

The increasing rate with increasing age, especially in men, is indicative of a feature found in many other studies in Olmsted County residents. In the elderly in Olmsted County, a specific diagnosis is more likely to be identified because of their proximity to medical care, unlike other tertiary medical centers, where patients must travel for greater distances. Other tertiary centers are more likely to publish their collective experience, but the serious problem of selection or referral bias is unrecognized and therefore usually ignored. Such selection bias is almost universal for the case series in nonpopulation-based referral centers. Likewise, we have noted increasing numbers of cases in the very elderly in this population-based study. The reasons are the same as the age trend just referred to.

The age-specific incidence rates increased in each decade of life after age 40 years in both men and women, except for a nonsignificant decrease after the eighth decade in women. No patients were younger than 40 years. This latter finding is similar to that in our referral patients with AL, in which only 1% of patients were younger than 40 years.

Most of the patients with AL in our referral practice were in the seventh decade of life, whereas the largest group of our Olmsted County patients were those in the eighth decade. This difference may be accounted for by the better surveillance and diagnoses provided for the elderly in Olmsted County and the lower proportion of elderly who are referred from outside the county.

Although the incidence of AL increased in the fourth decade of the study (1980 through 1989), the difference was not statistically significant. Some of this increase may be due to the more frequent use of immunofixation of serum and urine since 1980. The presence of an M-protein increases the suspicion of AL and is more likely to result in the biopsy of appropriate tissue and thus the diagnosis of amyloidosis. In addition, the visual screening of all serum and urine electrophoretic patterns in the Special Protein Laboratory is also helpful for detection of a small M-protein and subsequent investigation of the underlying cause.

This first population-based study of AL indicates that its incidence rate is approximately 8.9 per million person-years, it is rare before the age of 40 years, and its incidence rate increases with advancing age.

REFERENCES


Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989 [see comments]

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