Longterm Outcome of Amyloidosis Associated with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine the outcome of amyloidosis associated with juvenile idiopathic arthritis (JIA) in a hospital-based series.

Methods. Patient registers and amyloidosis biopsy files of the Department of Pediatrics of Rheumatism Foundation Hospital, the main tertiary center for inflammatory joint disorders in children in Finland, were scrutinized from 1976 to the end of 2003 to look for amyloidosis in patients under age 19 years. Medical records were reviewed and patients were interviewed by telephone. The causes of any deaths were obtained from death certificates.

Results. Twenty-four patients under age 19 years with biopsy-proven amyloidosis were found. As a sign of renal disease at the time of diagnosis of amyloidosis, 16 patients (67%) had proteinuria, but none had renal insufficiency. The 5-year survival rate of the series was 87.5% (95% CI 75% to 100%), and 10-year survival was 75% (54% to 92%). Ten patients (42%) out of the 24 died during a mean followup of 15.4 (range 1.5–27.6) years. The main cause of death was related to JIA in all patients but one. Patients treated with prednisolone alone from the diagnosis of amyloidosis onward had a mortality rate significantly higher than those taking disease modifying antirheumatic drugs and/or cytostatics ($p = 0.001$). At the end of followup, 14 patients (58%) were alive, 12 with normal renal function (3 of them had undergone renal transplantation), one had renal insufficiency, and one proteinuria. Proteinuria disappeared in 4 patients who were proteinuric (2 with nephrotic syndrome) at baseline, and their renal function remained normal. All the live patients had completed at least the 9 years of compulsory education, and 4 had academic degrees. Two female patients had delivered healthy children.

Conclusion. The outcome of JIA-associated amyloidosis is poor. However, renal disease regressed in some patients under vigorous treatment. Successful treatment makes an active life possible for these patients. (First Release Mar 15 2008; J Rheumatol 2008;35:907–12)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS AMYLOIDOSIS

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. It is an umbrella concept for a heterogenous group of diseases, with chronic arthritis of unknown cause as the common characteristic. The outcome of the different forms of JIA varies greatly. Until recently, the most common cause of death in Caucasian JIA populations has been amyloidosis[1]. However, data have been published suggesting decreasing incidence and better prognosis of amyloidosis[2-5]. According to data from the Finnish National Renal Registry for Kidney Diseases there was no change in the number of new cases proceeding annually to renal replacement therapy [dialysis, renal transplantation (RTP)] due to inflammatory rheumatic disease-associated amyloidosis from 1987 to 2002. Instead, the mean age of patients admitted to the registry has increased significantly (unpublished data).

Amyloidosis is a disorder that occurs as a complication of chronic inflammatory disorders. It occurs primarily in lymphoproliferative disorders, or as a complication of a wide range of chronic inflammatory illnesses such as JIA in susceptible individuals[2,6]. This form is also referred to as AA amyloidosis since the protein subunit of the amyloid fiber is amyloid A (AA). The persistently elevated serum concentration of the fiber precursor protein of amyloid A (SAA) is a prerequisite, but other, mainly unknown, factors are important in amyloidogenesis as well[7]. AA amyloidosis is practically the only amyloidosis type occurring in children with JIA. Amyloidosis is insidious and progressive, leading from an asymptomatic phase to nephrotic syndrome, kidney failure requiring renal replacement therapy, and finally death. Most often the cause of death is renal failure[8], but at times involvement of other organs, e.g., the gut, may be fatal.

Our series represents all subjects among roughly 3500 children with JIA seen at the Rheumatism Foundation Hospital (RFH) in the years 1976–2003 who developed amyloidosis

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before the age of 19 years. Altogether, 24 cases were found. Significantly, we noted that since 1991, no new cases of JIA-associated amyloidosis in childhood or in adolescence have been documented in Finland[9]. We will describe the prognosis of the 24 patients and the quality of life of the surviving patients.

MATERIALS AND METHODS

This series comprises patients with JIA according to the ILAR 2001 criteria[10], 24 subjects altogether, who were identified in the patient registers and amyloidosis biopsy files of RFH, with amyloidosis diagnosed before the age of 19 years, from 1976 onwards[9]. The medical histories of most patients (medication, operations, renal function, HLA typing, renal transplants) were checked either in the RFH records, or in those of the treating hospitals.

All surviving subjects were interviewed by telephone by one of the authors (AS) for details of marital status, fertility, number of children, type of residence, schooling, employment, other diseases, and joint prostheses. Patients were followed up until death or until the end of 2003. The data were collected in 2004.

Demographic and clinical characteristics of the 24 patients are shown in Table 1. The oligoarticular disease type in 3 patients at disease onset changed to polyarticular in 2 patients, and to juvenile spondyloarthropathy in one patient. Two patients had refused medication for JIA: one refused disease modifying antirheumatic drugs (DMARD), the other a change from sodium aurothiomalate to cytostatics. At the time of diagnosis of amyloidosis, 19 patients were under 16 years of age, the youngest being 7.5 years old.

The indications for searching for amyloidosis in the 24 patients were proteinuria (n = 15), goiter (n = 2), or continuously high disease activity as assessed by clinical condition and C-reactive protein (CRP) (n = 7). SAA concentrations were not measured. All the 24 cases were biopsy-proven, and the diagnoses were based on the demonstration of green birefringence in polarized light after Congo-red staining. Thirty-seven biopsies were performed altogether. The sites biopsied were subcutaneous fat (n = 8), buccal cavity (n = 10), gastrointestinal tract (n = 8), kidney (n = 9), and thyroidea (n = 2). Two or 3 biopsies at different locations were performed for 9 patients.

Table 1. Characteristics of 24 children with juvenile idiopathic arthritis (JIA) and secondary amyloidosis.

Characteristics	
No. of girls (%)	19 (79)
Age at symptoms, mean (range), yrs	4.7 (1–11)
Age at diagnosis, mean (range), yrs	5.1 (1–12)
Time from onset of JIA to diagnosis of amyloidosis, median (IQR), yrs	8 (4, 12)
Disease onset type, n (%)	
Oligoarthritis	3 (12)
Polyarthritis	10 (42)
Systemic	11 (46)
Disease course, n (%)	
Extended oligoarthritis	2 (8)
Juvenile spondyloarthropathy	1 (4)
Polyarthritis	10 (42)
Systemic	11 (46)
HLA-B27 present, n (%)	13/22* (59)
Rheumatoid factor present, n (%)	1 (4)
Antinuclear antibodies, n (%)	10 (42)
Erythrocyte sedimentation rate at diagnosis of amyloidosis, median (range)	81 (13–147)

* HLA-typing was not performed in 2 of the 24 cases. IQR: interquartile range.

At diagnosis of amyloidosis, 17 patients were taking one DMARD with prednisolone, 2 a combination of DMARD with prednisolone, and 5 patients were taking prednisolone alone (Table 2). Fourteen patients had undergone arthroplasties (2–9 operations per patient) by the end of 2003.

The underlying cause of death was determined from death certificates in accord with the internationally established norm. Autopsy had been performed on all except one.

Statistical analysis. Results were expressed as mean or median, range or interquartile range (IQR). The Kaplan-Meier curve was used to illustrate the information on the cumulative proportions of survival, and the difference between the groups was tested by a permutation-type log-rank test. The 95% confidence intervals of survival rate were obtained by bias-corrected bootstrapping (5000 replications).

RESULTS

At the time of the positive biopsy for amyloid, 18 (75%) of the 24 patients had clinical manifestations of amyloidosis, namely renal disorder (n = 16) and goiter (n = 2).

Renal disorder. At the time of the verification of amyloidosis, none of the 24 patients had renal insufficiency (Figure 1). There were 16 proteinuric patients, of whom proteinuria cleared completely in 4 (2 with nephrotic syndrome at baseline) and almost completely in one with nephrotic syndrome. Four of them were taking chlorambucil and one methotrexate (MTX) after the documentation of amyloidosis. Three of the 5 have been completely free of proteinuria ever since. Eight patients out of the 24 showed no signs of renal disorder in the beginning, but 2 of the 8 developed renal insufficiency later.

Renal biopsy was repeated after 2 to 15 years in 3 proteinuric patients whose proteinuria resolved. Amyloid material was still present in renal tissue in all of them, although initially positive rectal and/or subcutaneous tissue samples had turned negative for amyloid.

Seven patients altogether had undergone RTP — including 2 without signs of renal disease at the time of diagnosis of amyloidosis — after a mean of 12.4 (range 4–21) years from the diagnosis of amyloidosis. Four of them died, one during the operation, and 3 others in the course of the following 7 years. Of the transplanted kidneys of the 3, there was an early rejection in one, and one showed amyloid material in biopsy 6 years after RTP, 2 years before death. In the third case, the family did not consent to autopsy, and the kidney had not been biopsied before death.

At the end of followup, 14 patients were alive, 12 with normal renal function (3 of them with RTP), one had renal insufficiency and one proteinuria (the initial amount of 10 g/day decreased to 1.5–2 g/day). Hypertension needing treatment was documented in 42% of the live patients, in all but one in the post-biopsy period.

Comorbidities. Other disorders among the 24 patients after the diagnosis of amyloidosis were hypertension (n = 12), carditis (n = 2), sarcoidosis (n = 1), diabetes (n = 1), hypothyreosis (n = 2), depression (n = 1), subarachnoidal hemorrhage (n = 1), transient ischemic attack (n = 1), hyperuricemia (n = 1), chronic uveitis (n = 3) leading to blindness in one, glomerulonephritis (n = 1), and leukemia leading to death (n = 1).

Table 2. Treatment of 24 children with JIA and amyloidosis.

Therapy	Initial Therapy for JIA, n (%)	At Diagnosis of Amyloidosis, n (%)	After Diagnosis of Amyloidosis, n (%)
Drugs			
Hydroxychloroquine	21 (87)	3 (12)	1 (4)
Gold sodium thiomalate	14 (58)	6 (25)	2 (8)
Penicillamine	0 (0)	3 (12)	0 (0)
Azathioprine	0 (0)	3 (12)	3 (12)
Sulfasalazine	0 (0)	0 (0)	2 (8)
Methotrexate	0 (0)	2 (8)	3 (12)
Chlorambucil	0 (0)	0 (0)	8 (33)
Prednisolone	11 (46)	24 (100)	24 (100)
Strategy			
No drugs	0 (0)	0 (0)	0 (0)
Single therapy	7 (29)	0 (0)	0 (0)
Single therapy with prednisolone	6 (25)	17 (71)	17 (71)
Prednisolone alone	0 (0)	5 (21)	5 (21)
Combination therapy	6 (25)	0 (0)	0 (0)
Combination therapy with prednisolone	5 (21)	2 (8)	2 (8)

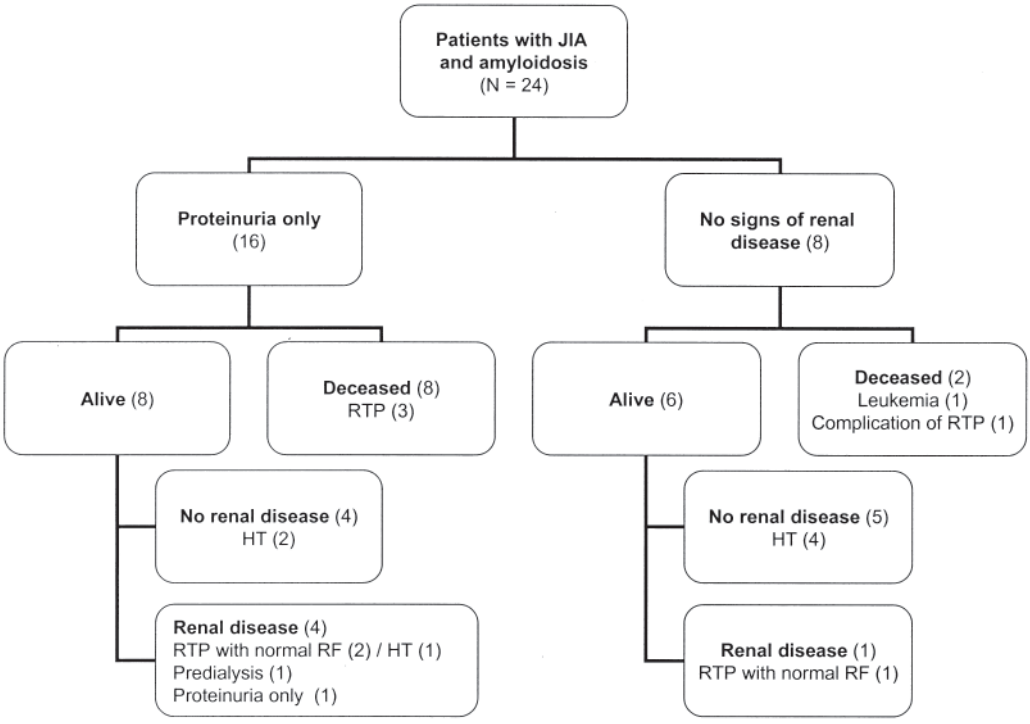

Figure 1. Outcome of 24 patients with juvenile idiopathic arthritis (JIA) and amyloidosis in relation to renal disorder. RTP: renal transplant. RF: renal function, HT: hypertension.

Survival. During a mean followup of 15.4 (range 1.5–27.6) years, 10 patients (42%) out of the 24 died. The 5-year survival rate of the series was 87.5% (95% CI 75% to 100%), and the 10-year survival was 75% (95% CI 54% to 92%) (Figure 2). Gender did not affect the number of deaths: 2 (40%) out of the 5 males and 8 (42%) of the 19 females died.

JIA was the main cause of death in 9 out of 10 deceased patients. The immediate causes of death were amyloidosis in 5 patients [renal insufficiency (n = 4) and hydropericardium (n = 1)] and infection (septicemia) in 3, all the latter with RTP. One death was perioperative. One patient died from leukemia with a 19-month history of chlorambucil treatment (cumulative dose 930 mg).

At some time during the disease course, all patients except

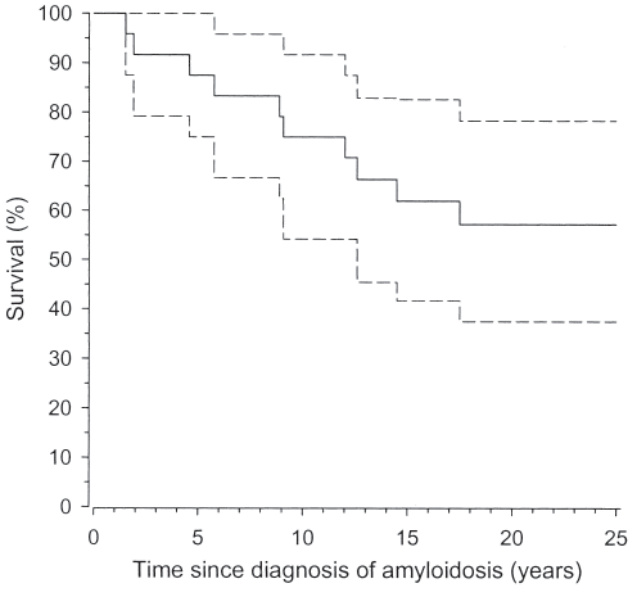

Figure 2. Product-limit survival curves for patients with juvenile idiopathic arthritis after diagnosis of secondary amyloidosis.

one had elevated serum concentrations of immunoglobulin G (IgG) up to 43.4 mg/ml. The one with normal IgG had very high serum IgA, 9.48 mg/ml. Three patients had IgA deficiency. These 3 were alive and free of proteinuria at the end of the followup 12 to 18 years after the diagnosis of amyloidosis. HLA-B27 test was performed in 8 out of the 10 deceased patients, and was positive in 3.

The median timespan from the diagnosis of amyloidosis of the 14 surviving patients was 20 (IQR 18, 23) years.

DMARD therapy and outcome. The overall drug therapy of the patients is shown in Table 2. At the time of verification of amyloidosis, drug treatment was changed in 14 patients. Chlorambucil (+ 6 months from the amyloidosis diagnosis) was started in 8 patients. Two of them died [survival 75% (95% CI 28%–97%)], one of amyloidosis, the other of leukemia, compared to the 8 of 16 [survival 48% (95% CI 20%–70%)] not treated with chlorambucil (p = 0.30). Altogether, 13 patients had some cystostatic therapy during the immediate post-biopsy period: azathioprine (n = 2) 2.5 to 2.9 mg/kg/day; chlorambucil (n = 8), 0.2 mg/kg/day; and MTX (n = 3) 7.8 to 13 mg/m^2/week. All patients who continued prednisolone monotherapy from the first documentation of amyloidosis onwards died, whereas survival was 73% (95% CI 48%–90%) in the patients in whom DMARD and/or cytostatics were continued or changed for another compound (p = 0.001). None of the 24 patients has been treated with biological drugs.

Social data of the patients surviving at the end of followup.
Education: Eight patients completed only the compulsory 9-year schooling requirement, 12 earned 1–6 additional years, and 4 completed an academic education of up to 17 years.
Working status: At the end of 2003, 9 patients were on a disability annuity due to JIA, 4 worked fulltime, and one was working on a university degree.
Marital status: Five patients were married, one divorced, 2 were engaged to be married, and 6 were single, 2 of them still living with parents.
Fertility: One female patient had delivered one child and another 2 children. The children are healthy and up to 20 years old. The woman with the 2 children had toxemia in both gravidities. She had nephrotic syndrome in the initial phase of amyloidosis; upon treatment with chlorambucil the proteinuria ceased, so she did not require RTP. Fertility was examined in 2 patients, and found to be normal in one female, whereas one male was found to be infertile. The remaining 9 patients were not planning to have children.

DISCUSSION

The Department of Pediatrics of RFH acts as the tertiary center for inflammatory joint disorders for children in Finland. It has traditionally cared for 60%–75% of patients with JIA in the country, i.e., practically all patients with severe disease have been treated here. Thus, most of the patients with a major risk for amyloidosis are probably under our supervision.

The current data show a highest prevalence of amyloidosis in the systemic-onset form of the disease, with incidence in British and German series of JIA-associated amyloidosis of 57% and 77%, respectively[2,11]. This shows a slight difference compared to our series, where the systemic and polyarticular type of disease have an almost equal frequency of amyloidosis, 46% and 42% of the cases, respectively. In 2 of our patients with polyarticular disease, the disease onset was oligoarticular, and one patient with oligoarticular onset developed juvenile spondyloarthropathy. HLA-B27 may act as a factor of chronicity in JIA[12], and so predispose to amyloidosis, as previously reported in Finland[13]. No clear effect of HLA-B27 could be seen on the prognosis of the condition in our current study, however.

The sex distribution (F:M) in JIA-associated amyloidosis varies between different studies, 1.8:1 in the 1970s in Finland[14], 1.6:1 in Germany[11], 1.1:1 in England (the largest one with 79 patients[15]), and our present study, 3.8:1. The general sex distribution among JIA patients in Finland is 2.4:1[16]. Male patients with amyloidosis fared worse than females in both the English[15] and the German[11] series. In our series, with 5 males and 19 females, mortality was of the same level. However, the small number of patients prevents us from drawing any firm conclusions.

There are scant data on the predisposing factors for amyloidosis in rheumatic diseases. In a Polish series with 67 JIA patients with amyloidosis, half the patients had immunoglobulin deficiency, and the phenomenon was associated with an almost 2-fold mortality compared to the rest of the group[17]. In our series, no patient had IgG deficiency. In contrast, the levels of IgG were high, as among the English patients[15]. In our series, all 3 patients with IgA deficiency were alive at the end of the followup.

Elevated blood pressure seems to be a frequent sequela in

JIA-associated amyloidosis. In our series, 42% of the live patients were taking antihypertensive medication. Almost half of the live English patients were hypertonic[2]. More than half the German patients with amyloidosis had elevated blood pressure at some time during the disease[11]. Many of the English and German patients already had hypertension at the diagnosis of amyloidosis[2,11], while all our patients except one developed hypertension during the followup.

The reversibility of amyloidosis has been described[7,15,18]. The disappearance of amyloid can be verified by biopsy, and also radiologically[19]. Our patients have not been systematically followed up in either way. However, the proteinuria disappeared in 4 of the 5 patients in whom it was initially documented. Three of them were taking chlorambucil and one MTX after the first documentation of amyloidosis. Three of the 4 patients have been free of proteinuria since then. However, renal biopsy still showed amyloid in the 3 of those patients in whom the procedure was repeated.

According to the reported 10-year survival rates, amyloidosis has a poor prognosis, which may, however, be influenced by cytostatic treatment (Table 3). None of the patients in the older Finnish series were treated with cytostatics[14], while a combination of azathioprine and glucocorticoids was common in the German series[11], with some patients even having had chlorambucil. David, *et al*[2] reported a 10-year survival of 80% in 57 patients treated with chlorambucil, but only 24% in 19 patients never treated with cytostatics. In Finland, during 2 consecutive 11-year periods (1969-79 and 1980-90), the percentage of amyloidosis as a direct cause of death diminished from 42 (10 patients) to 17 (4 patients), which could be indirectly attributed to a more active DMARD treatment policy[3]. The respective standardized mortality rates were 2.7 and 2.4.

In our series, chlorambucil was started in 8 patients within 6 months of the amyloidosis diagnosis. Two of them died — one of amyloidosis, with 6 years of proteinuria prior to the biopsy, the other of leukemia that was probably drug-induced — as did half of the 16 patients not treated with chlorambucil. Therapy with conventional DMARD and/or cytostatics was associated with an outcome better than was the case where a glucocorticoid was continued as the only therapy after confirmation of amyloidosis.

During a mean followup of 15 years in our series, 10 patients (42%) out of the 24 died, including 4 of the 7 with RTP. JIA can be considered the main cause of death in 9, amyloidosis being the immediate cause in 6, and septicemia in 3. One patient died of leukemia. At the end of 2003, 14 patients (58%) were alive; 12 had normal renal function, one had renal insufficiency, and one had proteinuria. Renal insufficiency is the most important life-threatening condition in JIA-associated amyloidosis. According to David and Woo[7], 84% of 79 JIA patients with amyloidosis died of renal failure. Infection was the second most common cause of death, usually due to bacterial septicemia.

In our series, half of the 16 originally proteinuric patients died. Among the remaining 8 patients without renal disease at the beginning, 2 developed renal insufficiency and received transplants. One of these 2 died due to a perioperative complication of RTP 9 years after amyloidosis was diagnosed, the other had normal renal function during the entire followup. Only 2 (25%) of the 8 patients originally free of proteinuria died, signifying a better prognosis.

In studies to date, little attention has been paid to the psychosocial aspects and quality of life of patients with amyloidosis, except in the study of David, *et al*[2], which dealt with their fertility state. In our series, patients did quite well in educational achievement. However, their working state remained poor. Fertility was not systematically assessed in our patients.

Although the mortality rate in our series of patients with JIA-associated amyloidosis was relatively high, our results suggest that vigorous drug therapy may reverse or prevent renal disease, ensuring patients' quality of life. In particular, the finding that the majority of the patients who were free of renal disorder at the time of verification of amyloidosis were still without signs of this manifestation at the end of the followup stresses the importance of early diagnosis of amyloidosis and the role of active antirheumatic therapy. In addition, our results show that in followup of patients with renal amyloidosis, renal biopsy is the only way to accurately confirm the regression of the amyloid accumulation. We look forward to seeing whether the prognosis of JIA-associated amyloidosis improves further with the use of biological drugs.

Table 3. Prognosis of 24 patients with JIA and amyloidosis based on the data of different series.

Country	No. of Patients	Period for Diagnosis of Amyloidosis	Cytostatic Treatment	10-year Survival Rate, %
Finland[14]	48	1950s–1970s	No	42
Germany[11]	60	1950s–1970s	Yes (a few patients)	35
UK[2]	57	1960s–1980s	Yes (chlorambucil)	80
UK[2]	19	1960s–1970s	No	24
Finland (present series)	24	1970s–1980s	Yes (a few patients)*	75

* Active disease modifying antirheumatic drug strategy was common in the post-biopsy period.

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