Title: Changing Epidemiology of AA Amyloidosis – Clinical Observations Over 25 Years at a Single National Referral Centre

Running head: Changing Epidemiology of AA Amyloidosis

Key words: AA amyloidosis, Rheumatoid arthritis, Juvenile idiopathic arthritis, Systemic autoinflammatory disorders, Biologics

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Abstract

Objective

Systemic AA amyloidosis is a serious complication of chronic inflammation, however, there are relatively few published data on its incidence. We investigated the changing epidemiology of AA amyloidosis over a 25-year period at a single national referral centre.

Methods

We conducted a retrospective study of all patients diagnosed with AA amyloidosis who had attended the centre between 1990 and 2014 inclusive. 625 patients were studied in three cohorts: C1: 1990-1997; C2: 1998-2006; C3: 2007-2014.

Results

Mean age at presentation increased from 46 in C1 to 56 in C3 ($p < 0.0001$). The proportion of South Asian patients increased from 4% in C1 to 17% in C3 ($p = 0.0006$). Comparison of underlying diseases between C1 and C3 revealed a reduction in patients with JIA from 25% to 2% ($p < 0.0001$), but an increase in patients with chronic sepsis due to IVDU from 1% to 13% ($p < 0.0001$), and uncharacterised inflammatory disorders from 10% to 27% ($p <0.0001$). More patients were in ESRF at presentation in C3 (29%) than C1 (15%) ($p = 0.0028$). Median age at death was later in C3 (62 years) than C1 (54 years) ($p = 0.0012$).

Conclusion

These data suggest both falling incidence and better outcome in AA amyloidosis over a quarter of a century, reflecting advances in therapeutics and overall management of complex chronic disease in an aging population. AA amyloidosis of uncertain aetiology presents an emerging major problem. Newer techniques such as next generation sequencing may aid diagnosis and effective treatment, thereby improving overall survival.

Key words

AA amyloidosis

Systemic amyloidosis

Epidemiology

Inflammation

Renal failure

Abbreviations

eGFR	Estimated glomerular filtration rate
ESRF	End stage renal failure
IBD	Inflammatory bowel disease
IVDU	Intravenous recreational drug use
JIA	Juvenile idiopathic arthritis
MDRD	Modification of diet in renal disease study
NAC	National Amyloidosis Centre
RA	Rheumatoid arthritis
SAA	Serum Amyloid A
SAIDs	Systemic autoinflammatory diseases
SAP	Serum amyloid P component
UK	United Kingdom

Systemic AA amyloidosis is a serious and life threatening complication of chronic inflammatory disorders. Despite the significant morbidity and mortality caused by AA amyloidosis, and the consequent cost burden to healthcare systems, there are relatively few published data on the epidemiology of AA amyloidosis.

Finnish studies report mortality from AA amyloidosis complicating rheumatoid arthritis (RA) ranging from 9 to 24% (1, 2). In a Spanish 9-year observational study of RA, 17% of deaths were attributed to AA amyloidosis (3). In other European studies, mortality from AA amyloidosis has been reported as much lower in comparison: 2% to 7% (4, 5). These studies demonstrate varying mortality associated with AA amyloidosis.

A Turkish study reported a change in incidence of AA amyloid detected on renal biopsy over time. Akse-Onal and colleagues (6) reported incidence of 12.1% in renal biopsies in Turkey between 1978 to 1990 and only 2% between 2000 to 2009 with no difference in age and gender distribution, age at onset, disease severity etc. between the two populations. This presumably reflects better disease awareness in general and widespread use of prophylactic colchicine in familial Mediterranean fever, historically the dominant cause of AA amyloidosis in this population.

A Swedish study identifying patients from hospital discharge and outpatient registers between 2001 and 2008 estimated an incidence of AA amyloidosis of 0.2 per 100 000, based on RA death rates (7). In 2013 an epidemiological study of systemic amyloidosis in England was conducted using combined data from the United Kingdom (UK) National Amyloidosis Centre (NAC) patient database and English death certificate data from the Office of National Statistics (8). The data suggested that only 48% of the UK caseload of patients with amyloidosis were referred to the NAC, producing an estimated incidence of AA amyloidosis in the UK of 0.166 per 100 000 in 2008.

In the UK, AA amyloidosis is the second commonest type of systemic amyloidosis diagnosed (AL amyloidosis being the commonest), and represents approximately 10.5% of new cases seen annually. Figure 1 shows the proportions of amyloid types in over 7000 consecutive patients reviewed at the UK NAC.

Aims

We sought to examine the changing epidemiology of AA amyloidosis over a period of a quarter of a century at a single national referral centre.

Patients and methods

Patients

All patients were under the care of a single national referral centre in the UK. We conducted a retrospective study of all patients first seen in clinic between January 1990 and December 2014. 625 patients were identified with confirmed AA amyloidosis. Patients were divided into 3 cohorts for analysis:

- Cohort 1: 153 patients who were first seen between 1990 and 1997
- Cohort 2: 236 patients who were first seen between 1998 and 2006
- Cohort 3: 236 patients who were first seen between 2007 and 2014.

Patients gave written informed consent for retrospective analysis and publication of their clinical data (Research Ethics Committee reference number 06/Q0501/42).

Diagnosis

Diagnosis of AA amyloidosis was made histologically (88%), or scintigraphically (12%) where biopsy was not possible (patient refused the procedure or the procedure was deemed too high risk) or tissue samples were not available or suitable for review. Other amyloid types were excluded by genetic analysis (for hereditary forms) and serum and urine protein electrophoresis and immunofixation (for AL amyloidosis). Patients were reviewed at six to 12 monthly intervals after diagnosis.

Histology and immunohistochemistry

The presence of amyloid in tissue sections was confirmed by a modified version of the alkaline-alcoholic Congo red method described by Puchtler *et al* (9). Formalin-fixed deparaffinised tissue sections, 6-8μm thick, were stained and then visualised under bright field and cross-polarised light. Positive controls, obtained from a known Congo red-positive composite block, were always processed in parallel. Immunohistochemical staining of formalin fixed de-paraffinised 2μm sections of amyloidotic tissue were performed using commercial monoclonal antibodies against SAA protein (Euro-Diagnostica, Huntingdon, UK) and AL kappa and lambda (Dako Ltd, Denmark House, Ely, UK) to determine the amyloid fibril type (10). Positive and negative controls were used in each run.

SAP scintigraphy

This nuclear medicine technique involves the intravenous injection of highly purified serum amyloid P component (SAP) which has been radio-labelled with the gamma emitting isotope ^{123}I; radio-labelled SAP localises rapidly and specifically to visceral amyloid deposits in

proportion to the amount of amyloid present (11). The technique has 100% diagnostic sensitivity in patients with systemic AA amyloidosis (12).

Renal function

Renal function was measured by means of serum creatinine and eGFR (by MDRD method), and creatinine clearance and proteinuria from 24-hour urine collections. Renal involvement by amyloid was defined as 24-hour urine protein leak >0.5 g/day, predominantly albumin, according to the International Consensus Criteria (13). End stage renal failure (ESRF) was defined as the initiation (or impending initiation) of renal replacement therapy (dialysis).

Statistical analysis

Mann Whitney tests and Kaplan-Meier analyses were performed using GraphPad Prism®.

Results

Whole-cohort characteristics

625 patients are described. 341 (55%) were male. The median age at first presentation at our Centre was 54 years (IQR 39 - 65). The underlying diseases were as follows: rheumatoid arthritis (RA) 28%, chronic infection 11%, seronegative arthritis 10%, systemic autoinflammatory diseases (SAIDs) 9%, juvenile idiopathic arthritis (JIA) 8%, inflammatory bowel disease (IBD) 5% and other causes (polyarteritis nodosa n=2, lymphoma n=3, Takayasu's arteritis n=2, spontaneous bovine encephalopathy n=1, mixed connective tissue disorder n=2 and familial paragangliomatosis n=1) totaling 2%. In 19% of patients the

underlying inflammatory disease was uncharacterised at diagnosis of AA amyloidosis. 300 patients reached ESRF, with 159 (53%) patients in ESRF at presentation. Median time to ESRF was 26 months. Whilst the number of new AA patients referred has been fairly stable during the last decade at an average of about 30 per year, referrals of patients with other types of amyloidosis have increased such that over the 25 year study period, the proportion of AA amyloidosis referrals has decreased as shown in Figure 2.

Comparison of cohorts

Age at referral, ethnicity and underlying disease

Mean age at presentation has significantly increased from 46 in the earliest cohort (cohort 1) to 56 in the latest cohort (cohort 3) ($p < 0.0001$). Ethnic group representation remains largely unchanged, although referral of South Asian patients has increased from 4% in cohort 1 to 17% in cohort 3 ($p = 0.0006$). The overwhelming majority of patients were Caucasian (Figure 3). A comparison of the underlying diseases between cohorts 1 and 3 reveals a reduction in patients with juvenile idiopathic arthritis (JIA) from 25% to 2% ($p < 0.0001$). Increased numbers of patients have presented with chronic infection due to intravenous recreational drug use (IVDU) – 1% in cohort 1 versus 13% in cohort 3 ($p < 0.0001$). There has also been a rise in AA amyloidosis of unknown aetiology from 10% to 27% ($p <0.0001$).The full comparison of underlying diseases between cohorts is shown graphically in Figure 4.

Development of end stage renal failure

In comparison with cohort 1, significantly more patients were in established ESRF at presentation in cohort 3 – 15% and 29% respectively ($p = 0.0028$). There was no difference in survival from ESRF between the cohorts at median follow up of 43 months (IQR 13 – 88).

Survival

There was no difference in overall survival between the cohorts. However, age at death was significantly different at a median of 54 years in cohort 1 and 62 years in cohort 3 ($p = 0.0012$) (Figure 5).

Discussion

In contrast to a threefold increase in referrals to the NAC of AL and other types of amyloidosis during the past decade, referral rates for AA amyloidosis have remained stable (Figure 2). This observation that AA amyloidosis is becoming less common may be a reflection of great advances in the use of biological agents in the effective treatment of the inflammatory arthritides. This has both reduced the incidence of AA amyloidosis, and when it does develop, has improved outcomes in what were until recently the commonest pathologies underlying AA amyloidosis. Whilst JIA and RA are no longer the main aetiological sources of AA amyloidosis, greater proportions of recent AA patients have uncharacterised underlying inflammatory disorders or chronic infection secondary to IVDU, compared to historical cohorts. Both patient groups pose challenges for clinical management, and it may be that these numbers represent a referral bias in seeking management advice due to expertise with off-licence biological treatments, rather than a true increase in incidence of these diseases. On the other hand similar series suggest this change in aetiology is more widespread (14). In addition, the older age of our most recent cohort may well reflect both the impact of better treatments such as biologics and more willingness to aggressively investigate and manage older patients. The significantly increased proportion of patients in ESRF in the latest cohort compared with the earliest is on the face of it both unexpected and disappointing. Possible explanations include

age-related decreased renal reserve resulting in more rapid loss of renal function in the presence of AA amyloidosis (15).

Although self-reported racial/ethnic group proportions have largely remained the same, with a preponderance of Caucasian patients, significantly more South Asian patients are represented in the recent cohort compared to the oldest. This change coincides with an increase in AA amyloidosis of unknown aetiology and suggests that novel as yet unrecognized pathology is contributing to chronic inflammation in this group. Clearly there may be other potential contributors such as an effect of increased migration over the study period, or perhaps greater use of the health service by a younger generation.

The mean age at presentation with AA amyloidosis in the recent cohort is significantly older than the earliest cohort. This again may be a reflection of the availability of effective biological treatments for inflammatory conditions. Whilst overall survival does not appear to have changed despite new effective therapies, age at death has increased significantly over the last 25 years, suggesting improved general management and supportive care including renal replacement, as well as more effective management of the underlying pathology.

Overall, these data suggest both falling incidence (corrected for improved diagnostic rates) and better outcome in AA amyloidosis over a period of two-and-a-half decades, reflecting advances in therapeutics and in overall management of complex chronic disease in an aging population. An unexpected issue to have appeared over this time is AA amyloidosis of uncertain aetiology which has proved challenging to manage empirically. We hope that newer techniques such as next generation sequencing and gene expression analysis may aid diagnosis and effective treatment of these ‘uncharacterised’ inflammatory disorders thereby improving overall survival.

Conflicts of Interest: None

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Figure Legends

Figure 1. Proportions of amyloid types diagnosed in 7747 consecutive patients seen at the UK National Amyloidosis Centre. WT ATTR = wild-type transthyretin amyloidosis (also known as senile systemic amyloidosis).

Figure 2. Change in number of referrals over study period by amyloid type. WT ATTR = wild-type transthyretin amyloidosis (also known as senile systemic amyloidosis).

Figure 3. Ethnic group proportions by cohort. The majority of patients were Caucasian. The proportion of South Asian patients referred increased significantly over the study period from 4% in cohort 1 to 17% in cohort 3 ($p = 0.0006$).

Figure 4. Comparison of underlying disease by cohort. Over the study period a reduction in patients with JIA from 25% to 2% ($p < 0.0001$) has been observed. More patients presented with chronic sepsis due to IVDU – 1% in cohort 1 versus 13% in cohort 3 ($p < 0.0001$). There has also been a rise in AA amyloidosis of unknown aetiology from 10% to 27% ($p <0.0001$).RA, rheumatoid arthritis; JIA juvenile idiopathic arthritis; SAIDs, systemic autoinflammatory disease; IBD, inflammatory bowel disease; IVDU, intravenous drug use.

Figure 5. Age at death. Although there was no difference observed in overall survival between the cohorts, age at death was significantly different at a median of 54 years in cohort 1 and 62 years in cohort 3 ($p = 0.0012$).