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Where has secondary amyloid gone?

There is a growing clinical impression that the incidence of amyloid secondary to rheumatoid disease is declining. Recent studies from Finland strongly support this impression.¹⁻³ The prevalence of amyloidosis in patients with rheumatoid arthritis who died in 1989 (about 6%)¹ was lower than in earlier studies.⁴ In a recent cohort of patients with early rheumatoid arthritis followed up for 8-14 years no one died from amyloidosis.² In a hospital for rheumatic diseases the annual number of biopsies positive for amyloid decreased from more than 60 in 1987 to fewer than 10 recently.³ The question arises whether this is a true decline of the incidence or a more concealed clinical presentation of this type of amyloidosis.

Development of AA amyloidosis

Secondary amyloidosis is nowadays called systemic AA amyloidosis. It is associated with chronic inflammation and results from systemic deposition of the acute phase reactant serum amyloid A protein (SAA) in a fibrillar structure. SAA behaves similarly to C reactive protein, being hardly detectable in normal situations and increasing quickly and dramatically during inflammation.⁵ In selected populations of patients with rheumatoid arthritis 5-20% of patients with longstanding disease will develop AA amyloidosis, depending upon the severity and duration of the arthritis in the population investigated.⁶⁻⁷

Although longstanding inflammation is necessary for the development of AA amyloidosis, it is not sufficient. Most people with a longstanding increase in SAA levels will never develop AA amyloidosis. In Europe AA amyloidosis is seen more often than in North America. Food, lifestyle, differences in drug treatment, other concurrent diseases, and genetic factors might be responsible for this difference. Genetic predisposition may be conditional for amyloid formation. One possible factor is homozygosity for SAA subtypes.⁸⁻⁹ Genetic research of diseases connected to the development of AA amyloidosis, such as familial Mediterranean fever,¹⁰⁻¹¹ autosomal dominant recurrent fever,¹¹⁻¹² and Muckle-Wells syndrome,¹³ has shown interesting results. The links to marenostin/pyrin (probably a neutrophil-specific transcription factor)¹⁰ and to tumour necrosis factor receptor 1¹² may provide insight into other factors related to the pathogenesis of AA amyloidosis.¹⁴

Clinical amyloidosis is defined as the presence of symptoms or signs suggestive of visceral involvement by amyloid.¹⁵ Most symptoms are caused by distortion of the normal tissue architecture. Examples are organ enlargement by massive amyloid deposition, easy bruising by weakening of the vascular walls, proteinuria by structural changes of the renal basement membrane, and loss of renal function by extensive glomerular deposits.

Preclinical phase of AA amyloidosis

Generally, it takes time before amyloid deposition gives rise to clinical amyloidosis. No data exist about the length of this phase of preclinical amyloidosis. Patients may die of other causes during this period and will be found only by chance at necropsy.¹⁻¹⁶⁻¹⁷ It is not clear whether these patients with rheumatoid arthritis simply had not had sufficient time to develop symptoms or whether they had a true asymptomatic form of AA amyloidosis—that is, the absence of symptoms or signs suggestive of visceral involvement. If a true asymptomatic form exists, its prevalence in rheumatoid arthritis may lie between 0.5%¹ and 14%.¹⁷ In a Spanish study of patients who had had rheumatoid arthritis for more than five years, clinical amyloidosis was found in 5%, preclinical amyloidosis in 3%, and (still) asymptomatic amyloidosis in 11% after 0 to 14 years of follow up.¹⁸

Regression of AA amyloidosis

Until recently, deposition of amyloid was thought to be irreversible. However, clinical symptoms (such as proteinuria) of some patients showed dramatic improvement when the underlying inflammatory disease had been cured effectively. Scintigraphic studies with radiolabelled serum amyloid P component, a constituent common to all amyloid deposits, demonstrated regression of amyloid deposits in some patients.¹⁹ The balance between deposition and removal of amyloid determines whether the amyloid load will progress or regress. The current therapeutic strategy in amyloidosis is to eliminate the supply of the precursor protein (SAA) by suppressing the acute phase response as much as possible. Apparently, physiological mechanisms can degrade amyloid, albeit at a rather slow rate. Elucidation of the process of amyloid degradation may open up the possibility of designing drugs or substances which can facilitate the breakdown of amyloid fibrils.²⁰⁻²¹

Possible reasons for the apparent decline of AA amyloidosis

TRUE DECLINE—THAT IS, A LOWER INCIDENCE OF ASYMPTOMATIC AMYLOIDOSIS

Successful eradication of tuberculosis, osteomyelitis, and other infectious diseases in the West has been followed by a sharp decline in the development of AA amyloidosis secondary to these diseases. This is why rheumatoid arthritis has become a relatively common cause of AA amyloidosis in the West during the past decades, rising from 35% to more than 60% of cases.²² If rheumatoid arthritis could be treated as successfully as the infectious diseases, one might expect a similar decline in the development of AA amyloidosis. Treatment of rheumatoid arthritis has been intensified in recent years,² by using more powerful drugs

earlier in the disease and in higher doses. More effective treatment of rheumatoid arthritis may reduce the cumulative supply of the acute phase protein SAA, thereby changing the balance from active deposition of the precursor protein to removal of amyloid.²³ A lag of 10 years or more is to be expected between intensification of treatment and a visible decline of amyloidosis.

In addition to the drug strategy, surgical possibilities for joint replacement have been expanded and the timing has been fixed at an earlier phase of the disease. The removal of substantial amounts of inflamed tissue during arthroplastic surgery helps to reduce the supply of the precursor protein SAA, thereby decreasing the deposition rate of AA amyloid.

A third cause of the declining incidence of AA amyloidosis in rheumatoid arthritis may be a decrease of the burden of comorbidity. In our oldest group of patients with rheumatoid arthritis and AA amyloidosis many had a past history of tuberculosis. One can imagine that the first period of inflammation caused by tuberculosis in youth induced a "primed state",²⁴ resulting in susceptibility to an accelerated deposition of amyloid during the second period of inflammation caused by rheumatoid arthritis later in life. Other forms of comorbidity, such as recurrent pulmonary and urinary infections,²⁵ can be controlled more effectively by antibiotic treatment than in the past. However, it should be noticed that a close relation between rheumatoid arthritis and pulmonary disease still remains, as illustrated by asymptomatic pulmonary disease in 70% of the patients during life²⁶ and by signs of pulmonary fibrosis found at necropsy in 35% of patients.¹⁷

SEEMING DECLINE—THAT IS, A LOWER INCIDENCE OF CLINICAL AMYLOIDOSIS

It seems unlikely that the group of patients with rheumatoid arthritis at risk for the development of amyloidosis has changed. Where patients have low grade inflammation it will take more time and patients will become older before amyloidosis becomes clinically manifest. The amyloid registry of our hospital seems to illustrate this. The median time between the onset of arthritis and the detection of clinical amyloidosis increased (although not significantly) by three years, from 16 years in the 1960s to 19 years in the 1990s.²⁷

Infectious diseases and non-infectious chronic inflammatory diseases differ fundamentally. A complete cure is seldom seen in the latter. Even with increasing therapeutic means, partial remission is more likely than complete remission in rheumatoid arthritis. Consequently, a moderate supply of the precursor protein SAA will remain. The balance between deposition and removal of amyloid will determine whether clinical features will become manifest. In some patients both processes may be approximately equal, thus stabilising the amyloid load without progression to clinical amyloidosis. Nowadays we may thus be confronted with a slower development of amyloidosis, a longer preclinical phase, and an insidious appearance of obscure symptoms, such as microalbuminuria, minimal change of renal function, splenic disease, and non-specific abdominal complaints.

NO DECLINE, BUT A DECREASE OF CLINICAL SUSPICION

No decline is visible in two recent studies of Japanese patients with rheumatoid arthritis.^{17, 28} AA amyloidosis was present in 18% of renal biopsy specimens in the period 1979–1988 and in 19% in the period 1989–1996.²⁸ No detailed information has been presented yet about a declining incidence in countries other than Finland.

In the study of early rheumatoid arthritis, the follow up of 8–14 years may have been too short for clinical

amyloidosis to develop. Because no post mortem was performed in 10 of the 25 patients (40%), preclinical or asymptomatic amyloidosis was not definitely excluded in this group.² In the other Finnish study of the hospital with a dramatically decreased number of biopsies positive for amyloid, the annual number of all biopsies also decreased sharply from 550 to 70 in this period.³ As a result, the percentage of biopsies positive for amyloid fell only from about 10% to 5%. Lack of suspicion, possibly owing to less conspicuous clinical features caused by a more subtle and insidious course of the AA amyloidosis, might have been a reason for the remarkable decrease in the number of all biopsies.

Classic features of clinical amyloidosis are proteinuria and renal failure. Other less familiar non-renal features, such as infections, bleeding, and bowel perforations, may also be life threatening. In a series of patients with AA amyloidosis, 22 of 63 patients (35%) died from such non-renal causes.²⁹ These features may already be present in preclinical amyloidosis, such as disease of the spleen (increased risk of serious infections) and of blood vessel walls of the gastrointestinal tract (increased risk of bleeding and perforation).

Conclusion

The clinician should be aware of a possible change in the way AA amyloidosis presents: a longer preclinical phase, a more insidious development of the classic symptoms and signs, and a change to less conspicuous features, such as an increased risk of infections, bleeding, and bowel perforations. The abdominal subcutaneous fat aspiration is a suitable tool to identify patients with preclinical amyloidosis.^{15, 18, 30} It takes little time, can be done during a visit to the outpatient clinic, is easy to perform, has a high yield, carries few risks, and can be repeated regularly. It should be noticed that patients in a steady state of (preclinical) amyloidosis remain at risk for a sudden acceleration of amyloid deposition in the case of a triggered acute phase response for reasons other than activity of their rheumatic disease—for example, during intercurrent infections or after major surgery.

We cannot give a final answer to the title question. Additional long term follow up data are necessary to decide whether the incidence of AA amyloidosis is really decreasing or whether it has gone "underground". It would therefore be helpful if the rheumatological society agreed on a core set of monitoring items for patients with longstanding rheumatoid arthritis, including monitoring for the development of amyloid—for example, by regular aspiration of subcutaneous fat in patients considered to be at risk.

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