CAUSES OF AA AMYLOIDOSIS: A SYSTEMATIC REVIEW

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INTRODUCTION

From a clinical perspective there is a need for a reliable and comprehensive list of diseases causing AA amyloidosis. This list could guide clinicians in the evaluation of patients with AA amyloidosis whom an obvious cause is lacking.

METHOD

In this systematic review a Pubmed, Embase, and Web of Science literature search was performed on causes of AA amyloidosis published in the last four decades. The diagnosis of AA amyloid was classified as proven, likely, possible or problematic. The strength of the association between the underlying disease and development of AA amyloidosis was defined as strong, weak, unclear or unlikely.

Proven diagnosis: Amyloid deposits had to be characterized histochemically by positive staining with Congo red, which also showed typical anomalous colours under polarized light, or the amyloid deposits had to characterized by electron microscopy [2].

Strong associations: Two or more publications of different groups that describe the association between a particulair disease and the development of AA amyloidosis, in which the diagnosis of AA amyloid is proven.

RESULTS

Table 1. *Strong associations with AA amyloidosis.*

	Disease		Disease
I	Chronic infection	II D	Gut
A	Bacterial infections		Crohn's disease
	Tuberculosis		Colitis ulcerosa
	Leprosy		Celiac disease*
	Whipple's disease	E	Other
	Osteomyelitis		Sarcoidosis
	Skin popping/injected-drug abuse		Obesity
	Chronic ulcers/decubitus	III	Hereditary
	Bronchiectasis	A	Inflammatory syndromes
	Abdominal infection/abscess*		Familial Mediterranean Fever
	Recurrent urinary infections		CAPS
B	Other infections		TRAPS
	Aspergillus*		Hyper IgD syndrome/ MKD
	Hepatitis B/C	B	Immunodeficiency
C	Diseases prone to infection		CVID
	Cystic fibrosis		Congenital/cyclic neutropenia
	Paraplegia	C	Metabolic
II	Chronic inflammation		Glycogen storage diseases*
A	Rheumatic diseases	IV	Hematologic diseases
	Rheumatoid arthritis	A	Neoplastic diseases
	Psoriatic arthritis		Waldenström's macroglobulinemia
	Seronegative spondyloarthropathy		Hodgkin's disease
	Juvenile idiopathic arthritis		Non-Hodgkin's Lymphoma*
	Gout	V	Tumours
	Systemic lupus erythematosus	A	Malignant
	Mixed connective tissue disease*		Diverse tumors, not specified
B	Vasculitis		Lung carcinoma
	Polymyalgia rheumatica		Mesothelioma
	Giant cell arteritis		Renal cell carcinoma
	Takayasu's arteritis	B	Benign
	Behçet's disease		Castleman's disease
C	Skin and subcutaneous tissue		Hepatocellular adenoma
	Epidermolysis bullosa	VI	Idiopathic
	Hidradenitis suppurativa*		Idiopathic*

**Associations new compared to earlier lists [1].*

RESULTS

Initially 4066 articles were found. Titles were excluded because of animal studies (n=434), language (n=242), conference abstract (n=243), no full-text publication (n=206) or non-AA type of amyloidosis/ irrelevant (n=2345).

A second search yielded another 199 articles, resulting in a final number of 795 full -text publications for analysis.

Hundred and fifty diseases were initially reported to be associated with the development of AA amyloidosis. The presence of AA amyloid was proven in 208 articles (26% of all) of which 140 (67%) showed a strong association with an underlying disease process. Disease associations were categorized and 48 were listed as strong (**Table 1**), 19 as probable, 23 as weak, and 60 as questionable.

CONCLUSIONS

- **AA amyloidosis is caused by different diseases inducing increased SAA serum levels, either directly by infections, inflammation or malignancies, or indirectly due to increased susceptibility to infections (e.g. CVID), or increased risk of chronic inflammation (e.g. glycogen storage disease).**
- **Based on the spectrum of identified causes, a pragmatic diagnostic approach is proposed for AA amyloidosis patients in whom an obvious underlying disease is lacking (Figure 1).**

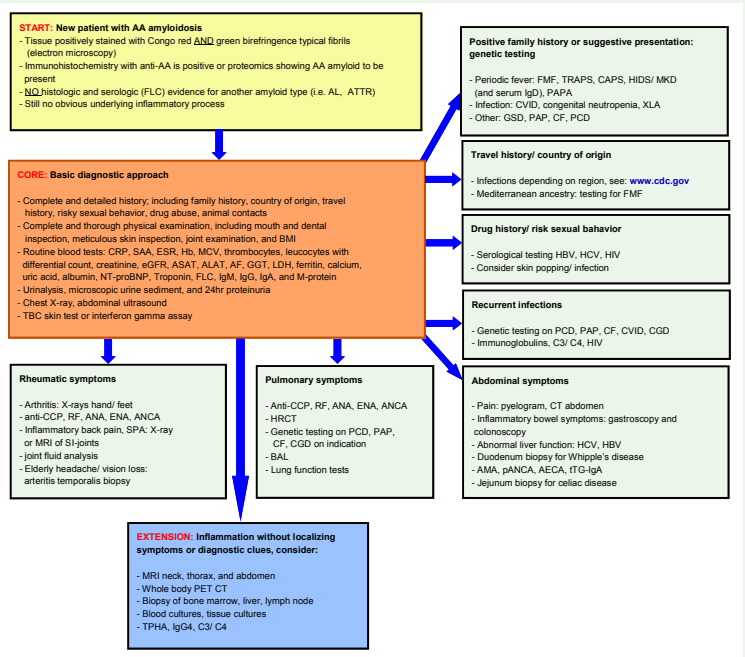

Figure 1. *Flowchart for diagnostic work-up to detect the underlying disease in a patient with a newly diagnosed AA-amyloidosis without an obvious cause (**yellow box**).*

First step is obtaining a complete history and performing a thorough physical examination, together with a core set of basic laboratory measurements and imaging (**orange box**).

Second step shows the possible investigations in seven directions guided by specific clues obtained from history or from symptoms (**green boxes**).

If localizing symptoms or diagnostic clues remain absent, a full search for the underlying inflammatory process is justified (**blue box**).

REFERENCES

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