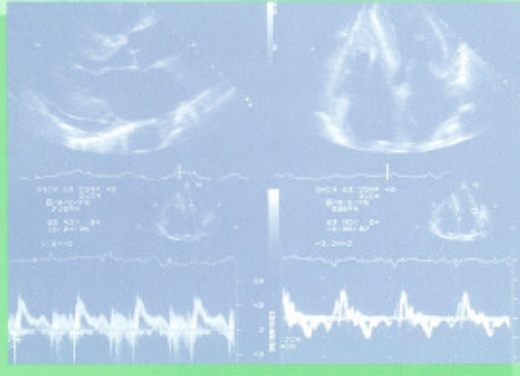


THE NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)[®]

THE PHYSICIAN'S GUIDE TO AMYLOIDOSIS



The National
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For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's Web site at www.rarediseases.org or call (800) 999-NORD or (203) 744-0100.

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals including *The NORD Guide to Rare Disorders* (Lippincott, Williams & Wilkins, 2003)

Contact NORD at:
orphan@rarediseases.org.



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into the light...[®]*

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Cover illustrations:
Features of AL amyloidosis—macroglossia,
bilateral periorbital purpura and a typical
echocardiogram.

INTRODUCTION

This booklet is the eighth in a series of free publications for physicians and other medical professionals. It is NORD's hope that patients and their families will benefit from this and other efforts to enhance awareness of the more than 6,000 rare diseases affecting an estimated 24 million Americans.

NORD is grateful to Rodney H. Falk, MD, Associate Clinical Professor of Medicine at Harvard Medical School and a clinical cardiologist at Harvard Vanguard Medical Associates in Boston, for writing this booklet.

The Amyloidosis Support Network, Inc., (www.amyloidosis.org), a non-profit organization dedicated to increasing awareness of this disease and improving the lives of those affected, provided an educational grant for this project.

This booklet was made possible by the fundraising efforts of the family & friends of David Jamieson of Massachusetts who passed away on July 18, 2004, due to AL amyloidosis. This booklet is dedicated to his memory and the valiant fight he fought.

WHAT IS AMYLOIDOSIS?

Amyloidosis is a systemic disorder characterized by the extracellular deposition of a protein-like material in multiple organs. The deposition of amyloid leads to progressive organ dysfunction. There are several types of amyloidosis, and they are classified according to their precursor protein. The commonest types of amyloidosis and the organs the most commonly involved are shown in the table. Briefly, primary (AL) amyloidosis is a plasma cell dyscrasia closely related to multiple myeloma. Familial amyloidosis is usually inherited as an autosomal dominant disease. It is most commonly associated with a mutant transthyretin (TTR) molecule, which is inherently unstable, and which breaks down to produce amyloid. Rarer mutations of apolipoprotein A1 and A2, gelsolin, fibrinogen A α -chain and cystatin C may also cause familial amyloidosis. Secondary (AA) amyloidosis is derived from the inflammatory protein serum amyloid A, and occurs in patients with chronic inflammatory disease such as the rheumatic diseases, chronic inflammatory bowel disease, tuberculosis or empyema. Senile amyloidosis, in which the amyloid is derived from wild-type (normal) transthyretin, is a slowly progressive disease that affects the hearts of elderly men. Amyloid deposits may occasionally occur in isolation without evidence of a systemic disease; isolated bladder or tracheal amyloid are the most common such presentations.

EPIDEMIOLOGY

It is estimated that there are between 1500 and 2500 new cases of AL amyloidosis annually in the United States. This is approximately 1/5 of the incidence of multiple myeloma and is similar incidence to that of Hodgkin disease or chronic myelocytic leukemia. As the prognosis of untreated AL amyloidosis is poor, the prevalence (total number of cases) of each of the latter two diseases is higher than that of AL. Familial and secondary amyloidosis are probably less common than AL amyloidosis, whereas senile amyloidosis is probably more common, but considerably underdiagnosed.

HOW DOES THE DISEASE PRESENT?

Amyloidosis is usually a multisystem disease resulting in a wide spectrum of clinical presentations. Consequently, a patient may present to, or be referred to, one of several subspecialists, most commonly a nephrologist, cardiologist or neurologist. While an individual subspecialist may see few cases during his or her professional career, recent advances in therapy have rendered early and precise diagnosis critical if the patient is to fully benefit. Thus, a high degree of awareness on the part of primary care and specialist physicians is of great importance. The common presentations

LIVER AND GASTROINTESTINAL TRACT

Some degree of hepatic involvement is common in AL amyloidosis. It is also common in AA amyloidosis but is not seen in transthyretin-related familial amyloidosis. In most cases, hepatic involvement is asymptomatic, despite hepatomegaly that may be prominent. Generally, the amyloid-infiltrated liver feels very hard and alkaline phosphatase is moderately or markedly elevated with normal or near-normal transaminases. Elevation of bilirubin is an ominous sign and may portend hepatic failure. Hepatic amyloidosis rarely occurs in isolation and is usually associated with organ involvement elsewhere.

Diarrhea in amyloidosis is most commonly related to autonomic dysfunction involving the bowel. Occasionally, amyloid deposits anywhere in the GI tract may result in gastrointestinal bleeding. Loss of taste, and a difficulty eating solid foods because of macroglossia, may contribute to weight loss, or weight loss may be a non-specific manifestation of the systemic disease. In patients with autonomic neuropathy, gastric emptying is impaired, resulting in a sensation of early satiety.

SOFT TISSUE AND SKIN

The dermatologic manifestations of AL amyloid may strongly suggest the diagnosis, particularly when other organ involvement suggests a systemic disease. Dermatologic involvement is almost exclusively limited to AL amyloid and consists of soft tissue, skin and vascular abnormalities. Periorbital purpura is a result of capillary fragility and is virtually pathognomonic of AL amyloidosis. It may appear after coughing, sneezing, or straining for a bowel movement. Not infrequently, purpuric lesions may arise after such simple actions as rubbing the eyelids. Soft tissue infiltration may cause macroglossia and hoarseness, although examination of the vocal cords may appear normal.

PULMONARY INVOLVEMENT

Amyloid deposits are commonly found in the lungs at autopsy of patients with AL or senile amyloidosis, but rarely cause any problems during life. Occasionally in AL, significant pulmonary infiltration may occur, resulting in a severe decrease in diffusing capacity. This almost invariably occurs in patients with co-existing significant cardiac involvement. Pleural effusions are quite common in patients with congestive heart failure due to amyloidosis, but large recurrent pleural effusions disproportionate to the degree of heart failure suggest pleural amyloidosis.

ENDOCRINE INVOLVEMENT

An elevation in TSH is very common in AL amyloidosis but overt hypothyroidism is rare. Adrenal infiltration is often seen at autopsy but frank adrenal failure is almost never seen.

DIAGNOSIS (see figure on page 7)

Tissue biopsy is the *sine qua non* of diagnosis. Amyloid deposits have a characteristic apple-green birefringence when stained with Congo red and viewed with a polarizing microscope. If the disease is suspected on clinical grounds, a biopsy of the involved organ will give the highest yield. Alternatively, staining of a subcutaneous abdominal fat pad aspirate frequently is positive in AL amyloidosis. Rectal biopsy as a diagnostic test for non-gastrointestinal amyloid is more invasive, and has a lower yield than fat pad aspiration and should not generally be used.

Once a tissue biopsy of amyloid has been established, it is mandatory to determine the type of amyloidosis. In AL amyloidosis, manifestations of a plasma cell dyscrasia will almost always be found. Serum and urine immunofixation should be performed, as this is much more sensitive than protein electrophoresis. A bone marrow biopsy, with appropriate immunohistochemical staining, will demonstrate a clonal population of plasma cells in 85 to 90% of cases. The recently-introduced serum-free light chain assay is a quantitative measure of the production of abnormal free light chains and it demonstrates disproportionate elevation of free kappa or free lambda in over 90% of cases of AL amyloidosis.

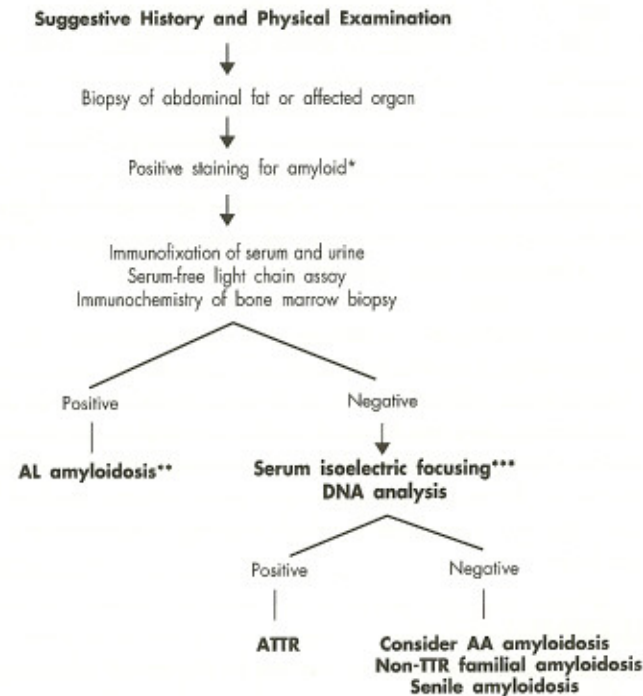
If these tests are negative, in the setting of a positive biopsy for amyloid, a non-hematologic form of amyloid should be suspected. Genetic testing of the transthyretin molecule can be performed. In the absence of mutations of transthyretin, very rare forms of familial amyloid may be present. However, if the patient is an elderly man with clinically isolated cardiac involvement, the most likely diagnosis is senile systemic amyloid (senile cardiac amyloid), a condition in which wild-type transthyretin is deposited in the heart.

TREATMENT

The type of treatment available is driven by the type of amyloidosis and the clinical state of the patient. Chemotherapy forms the cornerstone of treatment for AL amyloidosis. Various regimens have been studied but the commonest include melphalan given either orally or intravenously. In carefully selected patients, treated at centers with the appropriate experience, high-dose intravenous melphalan with autologous stem cell transplantation has a high degree of success in abolishing evidence of the plasma cell

dyscrasia. This is often associated with improvement in organ function. Not all patients can tolerate this aggressive regimen, particularly those with symptomatic cardiac involvement. Lower doses of intravenous melphalan without the need for stem cell transplant, dexamethasone, and other chemotherapeutic agents have been used to some success and thalidomide, lenalidomide (Revlimid) and bortezomib (Velcade) are undergoing clinical trials as adjunctive or primary therapies. Supportive therapy (treatment of congestive heart failure, attention to nutrition, treatment of autonomic neuropathy etc.) is a very important concomitant measure. Given the complexity of the disease, it is recommended that treatment be performed in the center with experience of amyloidosis, or at least that the patient should have an initial evaluation at such a center, with continued communication during treatment in the local community.

Figure: Flow diagram for the diagnosis of amyloidosis.



* Specialized stains for typing the amyloid are available, but are difficult to apply and should be performed only in centers skilled in the technique.

** If the clinical picture is inconsistent with AL amyloidosis or if there is a suggestive family history, testing/staining for other types of amyloid should be pursued, as an unrelated monoclonal gammopathy may coincidentally be present.

*** Screening test for mutant TTR performed in a few specialized centers.

Familial TTR amyloidosis is treated, if possible, by removal of the source of the abnormal TTR production. Since the dominant source is the liver, liver transplantation is currently the treatment of choice in carefully selected patients whose disease is not too far advanced. In senile amyloidosis, therapy is supportive but, both for this disease and for ATTR, pharmacologic therapies aimed at stabilizing the transthyretin molecule and thus preventing amyloid formation are being actively investigated. The mainstay of secondary amyloidosis treatment is therapy of the underlying disease. Renal transplant has been performed successfully for renal disease due to secondary amyloidosis. Eprodinate (Fibrillex) is a small molecule that inhibits the formation of amyloid fibrils, and which seems to have a modest clinical effect in patients with secondary amyloidosis.

RESOURCES

This resource section is designed to direct you to more information should you need it for yourself, the patient or the patient's family. The following services are available to help you.

PATIENT ADVOCACY ORGANIZATIONS:

ASN - Amyloidosis Support Network Inc.

www.amyloidosis.org

The ASN web site provides professional articles by leading researchers along with diagnosis & testing information. For patients, it includes the full range of information including patient education, support groups and case histories. ASN is dedicated to improving patient survivability and quality of life through earlier detection of the disease.

Email: info@amyloidosis.org

Tel: Toll-free at (800) 689-1238 or (770) 977-1500

ASG - Amyloidosis Support Groups Inc.

www.amyloidosisupport.com/

ASG oversees patient & family face-to-face and Internet-based support services.

Email: muriel@amyloidosisupport.com

Tel: Toll-free at 866-404-7539 or 630-350-7539

ARF - Amyloidosis Research Foundation, Inc.

www.amyloidosisresearchfoundation.org

This foundation has been established to raise funds for research to find the cause for amyloidosis and develop more effective means of diagnosis and treatment.

Tel: 248-673-1477

MAJOR AMYLOIDOSIS TREATMENT CENTERS

The following centers have amyloidosis practices where they conduct research and clinical trials.

Boston University Medical Center - Amyloid Treatment and Research Program
<http://amyloid.bu.edu/amyloid/Amyloid1.htm>
Tel: (617) 638-4317

The Mayo Clinic – Rochester MN
www.mayoclinic.org/amyloidosis/index.html
Tel: (507) 284-2111

Memorial Sloan Kettering – New York City
www.mskcc.org/prg/prg/bios/532.cfm
Tel: (212) 639-8086

OTHER U.S. PHYSICIANS WITH SPECIFIC CLINICAL EXPERTISE IN AMYLOIDOSIS:

Familial Amyloidosis. Merrill Benson, MD. Amyloid Research Group, University of Indiana, Indianapolis, IN.
www.iupui.edu/~amyloid
Tel. (317) 278-3426

Cardiac Amyloidosis. Rodney H. Falk, MD. Harvard Vanguard Medical Associates, Harvard Medical School, Brigham and Women's Hospital, Boston MA.
rfalk@partners.org, Tel. (617) 421-6050.

INTERNATIONAL AMYLOID CENTERS

Center for the Study and Cure of Systemic Amyloidosis, Pavia, Italy.
www.amiloidosi.it

National Amyloidosis Center, London, UK.
www.ucl.ac.uk/medicine/amyloidosis/nac/

OTHER RESOURCES

NORD – National Organization for Rare Disorders
www.rarediseases.org
Tel: (203) 744-0100 or (800) 999-NORD

Leukemia & Lymphoma Society
www.leukemia-lymphoma.org/hm_lls
Tel: (914) 949-5213 or (800) 955-4572

SELECTED REVIEW ARTICLES

Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid disease. *Biochimica et Biophysica Acta* 1753:11-22; 2005.
An excellent and comprehensive clinical overview of the amyloidoses.
Reprint request: centro.amiloidosi@smatteo.pv.it

Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *New England Journal of Medicine*. 349: 583-96; 2003.
A review of the basic mechanisms of the amyloidoses, including clinical aspects and illustrations.
Reprint request: centro.amiloidosi@smatteo.pv.it

Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PH, Merlini G, Moreau P, Ronco P, Sanchirawala V, Sezer O, Solomon A, Gateau G. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. *Am J. Hematol.* 79:319-328; 2005.
A well-referenced review of clinical features of AL amyloidosis by experts from the world's major amyloid centers.
Reprint request: gertz.morie@mayo.edu

Benson M. The hereditary amyloidoses. *Best Practice and Research Clinical Rheumatology* 17: 909-927; 2003.
A comprehensive and well-illustrated review of the hereditary transthyretin and non-transthyretin amyloidoses, their clinical features and treatment.
Reprint request: mdbenison@iupui.edu

Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 112: 2047-2060; 2005.
Detailed and well-illustrated review of the diagnosis, management and treatment of all types of cardiac amyloidosis.
Reprint request: rfalk@partners.org

Dember L. Emerging treatment approaches for the systemic amyloidoses. *Kidney International*. 68: 1377-90; 2005.
A general review of amyloidosis centering on targets for treatment, with an excellent "kidney focused" question and answer section.
Reprint request: ldember@bu.edu

To obtain additional copies of this booklet, contact NORD or the Amyloidosis Support Network.

