Thus, it is important to screen both for plasma cell disorders and for mutations in patients with amyloidosis. Variant TTRs can usually be detected by isoelectric focusing, but DNA sequencing is now standard for diagnosis of ATTR and other AF mutations.

TREATMENT ATTR AMYLOIDOSIS

Without intervention, the survival period after onset of ATTR disease is 5–15 years. Orthotopic liver transplantation replaces the major source of variant TTR production with a source of normal TTR. While liver transplantation can slow disease progression and improve chances of survival, it does not reverse sensorimotor neuropathy. Liver transplants are most successful in young patients with early peripheral neuropathy; older patients with familial amyloidotic cardiomyopathy or advanced polyneuropathy often experience end-organ disease progression despite successful liver transplantation. Progressive disease has been attributed to accumulation of wild-type TTR in fibrillar deposits initiated by the mutant.

The rate-limiting step in ATTR amyloidosis is dissociation of the TTR tetramer into monomer followed by misfolding and aggregation. TTR tetramers can be stabilized by thyroxine binding or by small molecules such as the non-steroidal anti-inflammatory drug diflunisal or the rationally designed small-molecule therapeutic tafamidis. A placebo-controlled randomized trial of diflunisal demonstrated a reduction in the progression of polyneuropathy and maintenance of quality of life in patients with a wide variety of ATTR mutations who received the "repurposed" diflunisal. Tafamidis tested in a similar fashion in patients with the V30M ATTR mutation failed to meet its primary endpoints, but tafamidis was approved by the European Medicines Agency since most secondary endpoints favored the drug. These agents are now being investigated for effects on cardiomyopathy, and in ATTRwt. *In vitro* data and serendipitous observations in patients suggest that ATTRm disease can be ameliorated by "trans-suppression," in which a T119M TTR variant stabilizes tetramers that also contain amyloidogenic subunits. Interestingly, in a large population study in Denmark, 0.5% of participants were heterozygous for the T119M allele, and this small group had higher levels of TTR in their blood, a reduced incidence of cerebrovascular disease, and a 5- to 10-year survival advantage compared with participants lacking this allele.

$A\beta_2M$ AMYLOIDOSIS

$A\beta_2M$ amyloid is composed of β_2-microglobulin, the invariant chain of class I human leukocyte antigens, and produces rheumatologic manifestations in patients undergoing long-term hemodialysis. β_2-Microglobulin is excreted by the kidney, and levels become elevated in end-stage renal disease. The molecular mass of β_2M is 11.8 kDa—above the cutoff of some dialysis membranes. The incidence of this disease appears to be declining with the use of newer membranes in high-flow dialysis techniques. $A\beta_2M$ amyloidosis usually presents as carpal tunnel syndrome, persistent joint effusions, spondyloarthropathy, or cystic bone lesions. Carpal tunnel syndrome is often the first symptom. In the past, persistent joint effusions accompanied by mild discomfort were found in up to 50% of patients who had undergone dialysis for >12 years. Involvement is bilateral, and large joints (shoulders, knees, wrists, and hips) are most frequently affected. The synovial fluid is noninflammatory, and β_2M amyloid can be found if the sediment is stained with Congo red. Although less common, visceral β_2M amyloid deposits do occasionally occur in the gastrointestinal tract, heart, tendons, and subcutaneous tissues of the buttocks. There is no specific therapy for $A\beta_2M$ amyloidosis, but cessation of dialysis after renal allografting may lead to symptomatic improvement.

SUMMARY

A diagnosis of amyloidosis should be considered in patients with unexplained nephropathy, cardiomyopathy (particularly with diastolic dysfunction), neuropathy (either peripheral or autonomic), enteropathy, or the pathognomonic soft tissue findings of macroglossia or periorbital ecchymoses. Pathologic identification of amyloid fibrils can be made with Congo red staining of aspirated abdominal fat or of an involved-organ biopsy specimen. Accurate typing by a combination of immunologic, biochemical, and genetic testing is essential in selecting appropriate therapy (Fig. 137-1). Systemic amyloidosis should not be considered an untreatable condition, as anti–plasma cell chemotherapy is highly effective in AL disease and targeted therapies are being developed for AA and ATTR disease. Tertiary referral centers can provide specialized diagnostic techniques and access to clinical trials for patients with these rare diseases.

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