ABSTRACT: Neuropathy is often a major manifestation of systemic amyloidosis. It is most frequently seen in patients with hereditary transthyretin (TTR) amyloidosis, but is also present in 20% of patients with systemic immunoglobulin light chain (primary) amyloidosis. Familial amyloid polyneuropathy (FAP) is the most common form of inherited amyloidotic polyneuropathy, with clinical and electrophysiologic findings similar to neuropathies with differing etiologies (e.g., diabetes mellitus). Hereditary amyloidosis is an adult-onset autosomal-dominant disease with varying degrees of penetrance. It is caused by specific gene mutations, but demonstration that a patient has one such mutation does not confirm the diagnosis of amyloidosis. Diagnosis requires tissue biopsy with demonstration of amyloid deposits either by special histochemical stains or electron microscopy. Transthyretin amyloidosis is treated by liver transplantation, which eliminates the mutated transthyretin from the blood, but for some patients continued amyloid deposition can occur from wild-type (normal) transthyretin. Presently, a study is ongoing to determine whether amyloid deposition can be inhibited by small organic molecules that are hypothesized to affect the fibril-forming ability of transthyretin. Proposed gene therapy with antisense oligonucleotides (ASOs) to suppress hepatic transthyretin synthesis is effective in a transgenic mouse model but has not yet been tested in humans.

THE MOLECULAR BIOLOGY AND CLINICAL FEATURES OF AMYLOID NEUROPATHY

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Neuropathy is a major feature of several types of systemic amyloidosis. It is most consistently seen in patients with hereditary transthyretin amyloidosis and is often present in patients with hereditary ApoAI amyloidosis caused by the glycine 26 arginine (Gly26Arg) mutation. Neuropathy is also a cardinal feature of hereditary gelsolin (Gel) amyloidosis. Peripheral neuropathy is not seen in reactive (AA, secondary) amyloidosis nor in most of the inherited amyloidoses characterized by renal, hepatic, or cardiac deposition. The most common cause of amyloid neuropathy is immunoglobulin light chain (AL, primary) amyloidosis, in which approximately 20% of patients have peripheral neuropathy and an even larger number have carpal tunnel syndrome. Because AL amyloidosis is a sporadic disease and little is known about the pathogenesis of immunoglobulin light chain amyloid neuropathy, we will focus on the hereditary types of amyloidosis for this discussion of the molecular biology and clinical features of amyloid neuropathy. However, AL amyloidosis needs to be considered in the differential diagnosis of patients with amyloidosis and neuropathy but with a family history insufficient to make a definitive diagnosis of a hereditary form of the disease.

TRANSTHYRETIN AMYLOIDOSIS

Transthyretin amyloidosis is the most common form of autosomal-dominant hereditary systemic amyloidosis. It is caused by mutations in transthyretin, a plasma transport protein for thyroid hormone and retinol-binding protein (RBP)/vitamin A. Transthyretin is a small, tetrameric protein that is synthesized mainly in the liver and is found in the blood as a dimer. The native tetramer is composed of four identical subunits, each containing 126 amino acids. Transthyretin amyloidosis is an autosomal-dominant disease that typically presents between the ages of 40 and 60 years, with a latency period of 10 to 15 years between mutation and manifestation of clinical disease. The most common mutation associated with transthyretin amyloidosis is the Val30Met mutation, which accounts for approximately 80% of cases. Other common mutations include the Met30Thr, Met23Thr, and Met6Val mutations, which respectively account for approximately 10% of cases each.

Since transthyretin is primarily synthesized in the liver, liver transplantation has been shown to be effective in treating transthyretin amyloidosis. Liver transplantation eliminates the mutated transthyretin from the blood, and for some patients continued amyloid deposition can occur from wild-type transthyretin. Presently, a study is ongoing to determine whether amyloid deposition can be inhibited by small organic molecules that are hypothesized to affect the fibril-forming ability of transthyretin. Proposed gene therapy with antisense oligonucleotides (ASOs) to suppress hepatic transthyretin synthesis is effective in a transgenic mouse model but has not yet been tested in humans.

Abbreviations: AGel, amyloid gelsolin; AL, immunoglobulin light chain amyloidosis; ApoAI, apolipoprotein AI; ASO, antisense oligonucleotide; CNS, central nervous system; FAP, familial amyloidotic polyneuropathy; Gel, gelsolin; FBP, retinol binding protein; SCA, senile cardiac amyloidosis; TTR, transthyretin

Key words: amyloid neuropathy; DNA testing; FAP, familial amyloidotic polyneuropathy; peripheral neuropathy; transthyretin

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thyretin is a single polypeptide chain of 127 amino acid residues. The transthyretin monomer (approximately 14,000 Da) folds to have an approximately 60% β-structure (Fig. 1). Four monomers associate noncovalently to form the tetrameric plasma transport protein (approximately 56,000 Da), which has binding sites for thyroxine in a central channel (T4) and surface receptors for RBP/vitamin A (Fig. 2, arrows). The transthyretin gene is localized to chromosome 18. It spans approximately 7 kb and has four exons. Exon 1 codes for a signal peptide of 20 amino acid residues and only the first three residues of the mature protein. Exon 2 codes for amino acid residues 4–47; exon 3, amino acid residues 48–92; and exon 4, 93–127. Essentially all plasma transthyretin is synthesized in the liver, but the protein is also expressed in the choroid plexus of the brain and the retinal pigment epithelium of the eye. Expression is present during embryonic development and throughout life, but transthyretin evidently is not essential for life because mice that have had the transthyretin gene inactivated show no abnormalities in development or fecundity.

Greater than 100 mutations in the primary structure of transthyretin have been discovered and the majority have been found in association with amyloidosis. Table 1 lists 98 amyloid-associated TTR mutations that have been reported, with some clinical and demographic features of each. In addition, there are a few newly identified TTR mutations that have not yet been entered into the scientific literature. No mutation has been reported for exon 1. Exon 2 has 37 mutations reported to be associated with amyloidosis; exon 3, 45; and exon 4, 16. Trans-
<table>
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<th>Codon change</th>
<th>Clinical features*</th>
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*Clinical features: AN, autonomic neuropathy; CTS, carpal tunnel syndrome; eye, vitreous deposits; LM, leptomeningeal; PN, peripheral neuropathy.
†Double-nucleotide substitution.
thyretin amyloidosis is an autosomal-dominant disease; only one mutant TTR allele is required to develop pathology. Most affected individuals are heterozygous for a pathogenic mutation and express both normal and variant TTR. The majority of the mutations are the result of a single nucleotide substitution in the transthyretin gene, although one is the result of the deletion of an entire 3-base codon (ΔVal122), and two of the amino acid substitutions are the result of double-nucleotide substitutions in a codon. The development of transthyretin amyloidosis is most likely the result of change in primary structure of the protein, but the disease must be modulated by a number of genetic and possible environmental factors. The variant TTR is present in the blood from the time of birth, but does not start to form amyloid until adult life. The reasons for amyloid formation at a particular point in adult life must be under control of factors not inherent to the mutant TTR gene itself and are likely to be related to the biochemistry of aging. Penetrance, the percentage of individuals who are gene carriers for a mutant transthyretin who develop clinical disease, varies considerably for the different mutations. In northern Sweden, the Val30Met mutation is associated with late-onset clinical disease (mean age, 55–60 years) and is reported to have less than 50% penetrance. The same mutation in northern Portugal is associated with earlier onset of clinical disease (30–35 years of age) and is now recognized to have a much higher penetrance, although early reports of elderly Portuguese patients without a family history of disease suggested a lower penetrance. The Ile84Ser mutation in an Indiana/Swiss kindred shows essentially 100% penetrance by age 50.

Of the approximately 100 amyloidosis-associated TTR mutations, many have been found in single individuals or families. Only a few mutations are present in extended kindreds and multiple loci worldwide. These include Val30Met, which is prominent in northern Portugal, northern Sweden, and Japan. This mutation, however, has been found in many other countries. The Thr60Ala mutation is prominent in the United States, but probably originated in Northern Ireland and has now been found in many countries with families of Irish descent. Leu58His is also frequently found in the United States in families originating in Germany, where it is also found. Probably the most prevalent transthyretin mutation in the United States is Val122lle. Approximately 3–4% of African Americans have this mutation, which causes late-onset restrictive cardiomyopathy that is rarely diagnosed in a timely manner. This mutation most likely originated on the west coast of Africa, where its prevalence is greater.

Some of the transthyretin mutations cause specific clinical syndromes, but there is considerable variation in disease presentation. Most produce sensorimotor polyneuropathy as a prominent feature and, for this reason, it has long had the name of familial amyloidotic polyneuropathy (FAP). The neuropathy usually starts with small-fiber dysfunction in the lower extremities, very similar to the neuropathy of diabetes mellitus, with lack of thermal appreciation being an early feature. Dysesthesias, however, may be prominent with or without varying degrees of pain. Motor function tends to be well maintained until the sensory neuropathy has advanced considerably. The level of sensory loss in the lower extremities slowly progresses from feet to ankles to legs to knees, at which time similar sensory symptoms usually present in the upper extremities. Autonomic neuropathy tends to occur relatively early in the course and results in sexual impotence in men, gastrointestinal motility problems, and bladder retention. Some men may have sexual impotence as their initial clinical symptom.

Nerve conduction studies can be a valuable tool for detecting peripheral nerve involvement. Localized abnormalities like median neuropathy at the wrist (carpal tunnel syndrome) can be differentiated from polyneuropathy based on the pattern of electrophysiological findings. Serial studies can help follow the course of peripheral nerve abnormality.

A group of amyloid patients referred to the Indiana University Amyloid Research Center in whom the transthyretin abnormality was known have been evaluated with conduction studies. Of the Val30Met and Thr60Ala patients, 60% showed abnormalities characteristic of polyneuropathy but a few had isolated median neuropathy at the wrist. Among these two patient groups, 40% were electrophysiologically normal when initially seen. In contrast, of the Ile84Ser patients with abnormal peripheral nerve conduction results, 40% had isolated median neuropathy at the wrist and 60% had polyneuropathy.

Considerable variability exists with transthyretin amyloidosis. Carpal tunnel syndrome is often an early feature and occasionally may be the only clinical manifestation. Vocal hoarseness can occur due to recurrent laryngeal nerve palsy, and the “scalloped pupil” deformity, which is essentially pathognomonic for FAP, is due to amyloid deposition in ciliary nerves of the eye (Fig. 3). Vitreous opacities are much more common, seen with approximately 20% of transthyretin mutations, and may be the first manifestation of FAP. Vitreous opacities may be a
part of the oculoleptomeningeal syndrome of amyloid deposition,10,23,70 or associated with amyloid cardiomyopathy without leptomeningeal involvement (Table 1).19,57 Oculoleptomeningeal amyloidosis may be restricted to intracranial and spinal fibril deposition and presents with symptoms of stroke, seizures, hydrocephalus, spinal cord infarction or, later, cerebral hemorrhage.

Historically, death was often the result of infected leg ulcers, osteomyelitis, or general inanition due to gastrointestinal dysfunction. It is now appreciated that restrictive cardiomyopathy is a major cause of morbidity and mortality in patients with transthyretin amyloidosis. The restrictive cardiomyopathy presents as generalized weakness and fatigue without the signs of fluid retention typically seen in other forms of cardiomyopathy. When significant restrictive cardiomyopathy develops in patients with concomitant autonomic dysfunction, orthostatic hypotension becomes a major clinical manifestation and maintenance of proper fluid balance is often a challenge. Cardiac arrhythmias may occur with atrial ventricular block, and sinus exit block is common. Atrial fibrillation usually occurs in the late stages of restrictive cardiomyopathy and adds to the congestive failure due to poor ventricular filling.

**Pathogenesis.** Several factors are important in the pathogenesis of transthyretin amyloidosis. First among these is the structure of the fibril precursor protein, because amino acid substitutions in the primary protein structure dictate the inheritance of the disease. Despite solution of the tertiary structure of a number of the mutant transthyretins by X-ray crystallography, it is not obvious how each change in primary protein structure leads to initiation of amyloid fibril formation.25 Indeed, it is known that normal transthyretin can cause tissue deposition of amyloid fibrils.78 This is most commonly seen as senile cardiac amyloidosis and suggests that transthyretin, which has a predominantly β-pleated sheet structure (Fig. 2), has an inherent tendency to form the β-structured fibrils that we call amyloid. In vitro studies also support the fibril-forming tendency of transthyretin. Several of the different mutant forms of transthyretin as well as normal transthyretin will form fibril structures in vitro when incubated at acidic pH.92,38 Although these physical chemical studies are valuable in studying the pathogenesis of transthyretin amyloidosis, in vitro fibril formation is a model of fibril formation and not a model of amyloidosis.

A second factor to consider in pathogenesis is metabolic processing of transthyretin. TTR is a very prominent plasma protein (20–40 mg/dl) and it has a plasma residence time of only 1–2 days.5,72 It must represent a significant burden to the catabolic mechanisms of plasma protein turnover. Much is known about the synthesis of transthyretin by the liver, but the sites of catabolic processing have not been well defined. There have been reports of metabolic processing by the liver, and the kidney is also usually a very significant site for catabolism of plasma proteins. Transthyretin amyloidosis, however, is most prominent in nerves and in the heart, organs that are not known for their catabolism of plasma proteins.

The question arises as to whether organs that have high degrees of protein catabolism such as the liver, which is rarely involved with transthyretin amyloidosis, and the kidney, which may be involved but not as extensively as one would expect, are relatively protected from the downstream metabolic events necessary for amyloid fibril formation and deposition. Biochemical analysis of tissue transthyretin amyloid fibrils suggests that proteolytic processing may well be an important factor in pathogenesis. Although full-length transthyretin protein may be present in amyloid fibril deposits, a large percentage of the protein has been proteolyzed to give fragments of the carboxyl-terminal portion starting at amino acid positions 49 and 52.8,17,41 Is this relevant to amyloid pathogenesis or an epiphenomenon? It should be noted that TTR amyloid fibrils isolated from tissues of patients heterozygous for a transthyretin gene mutation contain normal as well as the variant TTR protein. Because plasma TTR exists as a group of TTR tetramers with one, two, three, or four variant monomer subunits, it is logical that normal TTR might find its way to the final amyloid fibril structure. Indeed, tissue deposits of TTR amyloid usually contain only 65%–75% variant TTR; the rest is normal TTR.

Considerable data on in vitro fibril formation suggest that the TTR monomer is the intermediate moiety in the pathway to aggregation and fibril formation, and the stability of the tetramer is the most important factor in amyloid fibril initiation.42 This is difficult to reconcile with the fact that both normal and variant TTR monomers are found in the final end-product (the in vivo amyloid fibril). One would have to hypothesize parallel metabolic pathways for the two proteins (variant and normal monomers) and they would need to converge on the final step of fibril assembly. In addition, although TTR tetramer stability may well be important in amyloid pathogenesis, there are conflicting observations when experimental data are compared to observed biologic data.
For example, for the Leu55Pro TTR variant, which causes an early-onset, aggressive form of amyloidosis, the tetramer is thermodynamically unstable. However, the Val122Ile tetramer, which is also thermodynamically unstable, is associated with one of the latest-onset and slowest progressive forms of amyloidosis. Although the Val122Ile tetramer is less stable than the normal TTR tetramer, the age of onset of clinical disease and the rate of disease progression are very similar to those of senile cardiac amyloidosis, in which no TTR mutation is present.

The importance of other amyloid fibril components has not been addressed for transthyretin amyloidosis. It is known that glycosaminoglycans are integral parts of AA amyloid and Aβ Alzheimer amyloid plaques, but similar data have not been documented for TTR amyloidosis.

Another aspect of transthyretin pathogenesis that must be addressed is the selective involvement of certain organ systems. The peripheral nervous system is the most common site of amyloid deposition in the transthyretin amyloidoses (Fig. 4). The gastrointestinal tract is also usually involved, but restrictive cardiomyopathy is probably the leading cause of death. The kidney frequently has amyloid deposits, but clinically significant renal amyloidosis is not as common in transthyretin amyloidosis as in AA or AL amyloidosis. Although amyloid deposits occur in blood vessel walls throughout the body, the spleen and hepatic parenchyma do not have amyloid deposits.

In peripheral nerve, amyloid deposits start around perforating arterioles (Fig. 5A). This deposition occurs in a sporadic fashion and, in advanced stages, large globular deposits of amyloid are seen displacing nerve fibers (Fig. 5B). At this stage, severe demyelination and loss of nerve fibers are seen (Fig. 5C). Figure 5A–C shows postmortem sciatic nerve specimens; similar findings are seen in biopsies of sural or other sensory nerves done for purposes of diagnosis (Fig. 5D). In the few studies that have been done on dorsal root ganglia, fibril deposition and neuronal loss appear to be an important part of the peripheral neuropathy. Similarly, little attention has been paid to the autonomic nervous system, although detailed studies revealed amyloid deposition within autonomic ganglia, nerve trunks, and adjacent vascular structures. In leptomeningeal amyloidosis, deposits were seen in vascular and surrounding connective tissue structures.
leads to a clinical presentation with cerebral infarcts or, in later stages, cerebral hemorrhage. Infarcts may involve basal ganglia and the spinal cord. Although not proven, the amyloid fibril precursor of leptomeningeal amyloidosis is probably synthesized by the choroid plexus.\textsuperscript{15,63}

Patients dying from leptomeningeal amyloidosis have been found to have little or no amyloid deposition in other organ systems. Transthyretin amyloid in the vitreous of the eye is probably the result of synthesis by the retinal pigment epithelium.\textsuperscript{6} The predilection for fibril formation in the vitreous of the eye is not clear. The mechanisms involved in amyloid deposition in the vitreous may be similar to peripheral nerve or cardiac pathology, but an intriguing variation is that amyloid fibrils in the vitreous are greatly enriched (approximately 90\%–95\%) in variant TTR compared to the proportion (60\%–65\%) in nerve and cardiac tissue of heterozygotes.\textsuperscript{41}

Vitreous opacities are found with approximately 20\% of the known amyloid-producing TTR mutations and may be seen in conjunction with leptomeningeal amyloidosis.\textsuperscript{6} This may, however, be found with other mutations that primarily cause peripheral neuropathy or cardiomyopathy.

**APOLIPOPROTEIN AI (ApoAI) AMYLOIDOSIS**

Twelve different mutations in the ApoAI gene have been associated with systemic amyloidosis.\textsuperscript{2} The amyloidosis of only one of these mutations, however, has been shown to cause peripheral neuropathy. This ApoAI mutation, Gly26Arg, was first described by Van Allen et al., in a family residing in Iowa.\textsuperscript{73} Unlike transthyretin amyloidosis, the main clinical feature of ApoAI amyloidosis is renal amyloid deposition,
Amyloid Neuropathy

and death is usually caused by azotemia. Other organ involvement, including liver, spleen, and occasionally heart, has been seen in this syndrome. The renal amyloid deposition is unlike most cases of AL and AA amyloidosis, which usually cause significant proteinuria from glomerular fibril deposition. In ApoAI amyloidosis, amyloid deposits are predominantly in blood vessels and medullary structures. Proteinuria is usually very limited and nephrotic syndrome does not develop.

ApoAI amyloidosis is an adult-onset autosomal-dominant disease. In the Iowa kindred the first clinical manifestation appeared most commonly between age 30 and 40 years, but some individuals were affected by their late 20s, and others after 50. Most of the patients presented with neuropathic symptoms, but some were initially identified with renal failure. In most subjects, the neuropathy and renal failure were slowly progressive, with death occurring approximately 10 years after initial presentation. The disease duration varied from a few months to as long as 25 years.

Clinically, the neuropathy of ApoAI is very similar to transthyretin amyloidosis. It usually starts with sensory changes in the lower extremities. This is progressive and eventually involves the upper extremities. Weakness in leg muscles and foot drop often occur early in the disease. Impotence is a common feature in men. Ataxia, absent muscle stretch reflexes, and muscle atrophy are common as the disease progresses, and the patient may eventually become tetraparetic. Despite the extensive neuropathy, death is usually related to renal insufficiency.

A number of families have been described with ApoAI Gly26Arg amyloidosis and not all have neuropathy as part of their clinical picture. The reason for this is not known, nor is it known why the systemic amyloidoses caused by other mutations in ApoAI are not associated with peripheral neuropathy. In the Iowa kindred, neuropathy seems to have been delayed in the most recent generation; several individuals have begun to have neuropathy, but only after significant renal impairment was documented.

Amyloid deposition in neural structures with this form of amyloidosis was well described by Van Allen et al. and is very similar to the pathology of transthyretin amyloidosis. Large deposits of amyloid are found in peripheral nerves with displacement of nerve fibers. Extensive deposition is present in dorsal root ganglia. The leptomeninges around the spinal column and the brain show amyloid deposition, but, as with transthyretin, the central nervous system (CNS) parenchyma is not involved. Intracerebral hemorrhage has not been described with ApoAI amyloidosis. Leptomeningeal deposition is probably the cause of elevation in spinal fluid protein, which may exceed 200 mg/dl. Vitreous opacities are not part of this syndrome.

Pathogenesis. Mutations in the ApoAI gene, present as a single copy on chromosome 11 (11q23), are the cause of this form of amyloidosis. It is an autosomal-dominant disease and all affected subjects identified to date have been heterozygous for 1 of the 12 known mutations. Degree of penetrance has not been established but is probably greater than 50% of gene carriers. Both normal and variant ApoAI are found in blood. ApoAI is mainly contained in the high-density lipoprotein portion of plasma, as are SAA and ApoAII, two other amyloid precursor proteins. Pathogenesis appears related to incomplete degradation of the abnormal ApoAI, which normally is a single polypeptide chain of 243 amino acid residues. The amyloid deposits contain only the amino-terminal 83–93 amino acid residues of the protein. Despite the fact that patients are heterozygous for the variant ApoAI, there is no evidence that normal ApoAI contributes to fibril formation. With the neuropathic Gly26Arg protein, only the variant peptide is found in amyloid fibrils. Because ApoAI is mainly an \( \alpha \)-helical apolipoprotein, major reconfiguration of the amino-terminal portion of this molecule must occur in order for it to be incorporated into the \( \beta \)-pleated sheet structure that is typical of amyloid fibrils. As with transthyretin, there is good evidence that the variant ApoAI has an increase in metabolic rate. Studies with radiolabeled ApoAI have shown that the Gly26Arg protein has approximately half the plasma residence time of wild-type ApoAI. This indicates an increase in the catabolic rate of the variant protein, and it is hypothesized that this increased intracellular degradation leads to generation of the pathologic amino-terminal peptide.

GELSOLIN AMYLOIDOSIS (AGel)

The neuropathy of gelsolin amyloidosis starts as a progressive cranial neuropathy in middle age (approximately 40 years of age) and may be followed much later by peripheral neuropathy involving the limbs. The disease is first manifest as lattice corneal dystrophy, often by age 20–30. This unusual association is typical of AGel amyloidosis and makes diagnosis of the condition relatively easy.

Amyloid formation is the result of a mutation (Asp187Asn) in plasma gelsolin, an actin-modulat-
ing protein. Most patients are heterozygous for this mutation and have modest involvement of internal organs, mostly vascular. Individuals homozygous for the mutation may have severe systemic disease with renal failure. A second mutation in gelsolin (Asp187Tyr) has been described and gives a similar phenotype. There are few patients with AGel in the United States and Japan; most affected families are in southwestern Finland.

DIAGNOSIS OF AMYLOID NEUROPATHY

The diagnosis of any type of amyloidosis is made by tissue biopsy. The biopsy may be from a clinically affected organ such as heart, nerve, kidney, or liver, or, for systemic amyloidosis, a nonspecific site such as rectal mucosa, abdominal fat, or gingival or minor salivary gland. Occasionally, systemic amyloidosis will be detected as an incidental finding on bladder, prostate, or gastric biopsies. The greatest impediment to making a timely diagnosis is lack of consideration of amyloidosis in the initial evaluation of the patient. This is true for cardiac and renal amyloidosis where more common pathologic conditions cause similar organ dysfunction. This is also true in the neuropathic forms of amyloidosis.

Once the diagnosis of amyloidosis is considered, a rectal biopsy or abdominal fat aspirate may demonstrate amyloid deposition, but many patients require nerve biopsy to confirm the specific neuropathology (Fig. 5D). The sural nerve is most often used for diagnostic biopsy. It is purely sensory and, by the time biopsy is considered, the degree of sensory loss to the foot is usually such that further loss of sensation from the biopsy is well tolerated. In light of the spotty nature of amyloid deposition, however, a sural nerve biopsy that does not demonstrate amyloid deposits should not be taken as conclusive evidence that amyloid is not the cause of the neuropathy (Fig. 6). At this point, consideration of other organ systems should be undertaken: Are there associated signs of cardiomyopathy, renal disease, autonomic dysfunction, hypotension, erectile dysfunction, or alternating constipation and diarrhea?

After the diagnosis of amyloidosis is made, for the patient with neuropathy, the most important question is whether this is an hereditary form of amyloidosis or a sporadic immunoglobulin light chain (AL) primary amyloidosis. AL amyloidosis frequently causes carpal tunnel syndrome, and 20% of patients with AL will present with peripheral neuropathy. On nerve biopsy, there are no distinct features to differentiate hereditary amyloidosis from AL amyloidosis (Fig. 7A). Pathogenic mechanisms for initiation of amyloid deposition in endoneurial vascular structures are probably similar (Fig. 7B).

Immunohistochemistry with specific antibodies may be helpful, but unfortunately this technique is not completely reliable. The demonstration of a monoclonal plasma cell dyscrasia and presence of monoclonal immunoglobulin protein in serum or urine in approximately 80% of AL patients helps to distinguish these patients from those with hereditary syndromes.37

For hereditary neuropathic amyloidosis, family history can be very important, but is often not sufficient to confirm a diagnosis. Lack of penetrance and advanced age of onset of some of the transthyretin amyloidoses, as well as variable expression of the disease, hinder timely diagnosis. In rare cases de novo mutations in transthyretin cause amyloidosis. Of the hereditary amyloid neuropathies, gelsolin amyloidosis is the easiest to detect because all affected individuals have lattice corneal dystrophy from an early age. Careful ophthalmologic examination will reveal this pathognomonic sign. Neuropathy associated with the ApoAI Gly26Arg mutation is found in patients whose primary disease is renal and, unlike the typical AL amyloidosis patient, renal disease is associated with little proteinuria and presents as progressive azotemia. Transthyretin amyloidosis is the most frequent cause of hereditary amyloid neuropathy, and the entity that most often must be distinguished from immunoglobulin (AL) amyloidosis.

Most of the mutations in transthyretin that have been associated with amyloidosis cause some degree
of peripheral neuropathy. Neuropathic symptoms usually occur early in the disease process but may remain mild for an extended period of time. By the time the patient seeks care from a neurologist, there are often signs of other system manifestations, such as enteropathy or cardiomyopathy. The mainstay of diagnosing this disease is DNA testing, which will usually demonstrate one of the known mutations (Table 1). Occasionally, a new mutation will be found by direct DNA sequencing and correlation of disease and genetics will be needed. DNA testing is now available commercially as well as in a few amyloid research laboratories. If a patient has a family history of transthyretin amyloidosis and the family mutation is known, a specific test can be ordered to determine whether the patient is a carrier of this mutation. If a family mutation is not known, full TTR DNA sequencing is recommended. Ordering a panel of the most frequent TTR mutations will not necessarily exclude the diagnosis and may be a great disservice to the patient with a new mutation.

DNA sequencing for gelsolin and ApoAI mutations is not commercially available. Help from an amyloidosis research laboratory is recommended. These DNA tests are easily accomplished, but these types of amyloidosis are too uncommon to generate any great commercial interest.

Treatment. Therapy for hereditary amyloidotic neuropathy involves both specific and nonspecific measures. Nonspecific measures include treatment of the painful neuropathic symptoms. Treatment with gabapentin, amitriptyline, and more recently, pregabalin, may be effective but efficacy is unpredictable and, even when a drug is initially effective, the response may change as the neuropathy progresses. Alternating constipation and diarrhea are common manifestations of transthyretin amyloidosis. Addition of fiber to the diet to increase bulk of stool may be efficacious. Occasionally, alteration of gastrointestinal flora by antibiotics is effective, but often agents such as loperamide are required to slow bowel function. In severe cases, tincture of opium may be necessary. Urinary bladder retention occasionally requires training in self-catheterization. Newer agents for erectile dysfunction may help some men with autonomic dysfunction.

The only specific therapy for transthyretin amyloidosis is orthotopic liver transplantation. The basis for this form of therapy is to rid the plasma of mutated transthyretin, which is synthesized by the liver. Since the first patient received this therapy in 1990, greater than 1200 liver transplantations have been accomplished. Statistical analysis indicates that patients with the Val30Met mutation are most likely to benefit and have 80% survival at 5 years. Patients with other transthyretin mutations, however, do not fare as well and show a 5-year survival of only 55%–60%. Many patients, especially those with TTR mutations other than Val30Met, have progression of disease after liver transplantation. Biochemical analysis of amyloid from tissues of patients who died after having a liver transplant indicates that this is the result of continued amyloid deposition from wild-type TTR. It has been suggested that liver transplantation early in the course of disease should be considered, but it is still unknown whether this
would increase the overall time of survival. Nutritional status is an important factor in determining longevity after liver transplantation. As far as peripheral neuropathy is concerned, there is only one report documenting regeneration of nerve fibers on nerve biopsy after liver transplantation.33 At the present time, there is a study to determine whether diflunisal, a modified salicylate nonsteroidal anti-inflammatory drug, will alter the progression of TTR in amyloidosis. The study is based on the demonstration that small organic molecules such as diflunisal bind to the transthyretin tetramer and thermodynamically stabilize the structure. This form of therapy has not been tested in an animal model, but because diflunisal is marketed as a nonsteroidal anti-inflammatory drug, it has passed many of the safety requirements required for new drug approval. Vitrectomy may be considered a specific therapy for transthyretin amyloid in the eye; although usually effective, it is really a mechanical means of restoring visual acuity. Amyloid deposition may recur after vitrectomy and require repeated surgery. It is important to remember that these patients have increased risk of retinal detachment and many develop glaucoma after vitrectomy. They need to be monitored closely for changes in intraocular pressure. At the present time there is no evidence that orthotopic liver transplantation alters the course of oculooleptomeningeal amyloidosis.

Orthotopic liver transplantation has also been accomplished in a number of patients with ApoAl Gly26Arg amyloidosis and, although apolipoprotein levels in the blood only decrease by approximately 50%, disease progression seems to be favorably altered. As most of these patients underwent combined liver and kidney transplants, and it is usually the slowly progressive renal disease that determines the patient’s prognosis, it is difficult to be certain whether the generalized amyloidosis is favorably affected. Recently, some patients with only modest renal impairment received liver transplantation alone. Close longitudinal evaluation of these patients may reveal more clearly the efficacy of liver transplantation for this disease.

For gelsolin amyloidosis the only effective therapy to date is corneal transplantation. This is very effective and can be repeated if the amyloid deposits infiltrate the new cornea. Plastic surgery can be effective in treating the cutis laxis and blepharochalasis, which are the result of bilateral facial palsy, but there is no specific therapy for this disease. Gelsolin is an essential protein for actin function and treatments aimed at eliminating its production are not likely to be tolerated.

It is obvious that specific treatments are needed, especially for transthyretin amyloidosis. Recently, studies in mice transgenic for the human Ile84Ser TTR mutant gene have demonstrated suppression of hepatic TTR synthesis by antisense oligonucleotides (ASO). Whether this will be the basis for treatment of TTR amyloidosis, either FAP or senile cardiac amyloidosis (SCA), must await safety and efficacy testing. Similar gene therapy approaches have been proposed using ribozymes that suppress TTR expression in hepatic cell cultures. Also, recent studies on targeted conversion of the TTR gene have demonstrated the feasibility of this approach. These studies have not progressed to the point that a therapeutic agent for TTR amyloidosis can be predicted in the near future. Most important is the development of an animal model to test any new form of therapy in a timely fashion, because the human disease is caused by so many different mutations with various phenotypes and usually has a slowly progressive but ingravescent course.

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