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Chapter

Non-Alzheimers Amyloidoses of the Neurological System: Cerebral Amyloid Angiopathy and Familial Amyloid Polyneuropathy

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Abstract

Amyloid deposition plays a significant, albeit overlooked, role in neurologic disorders. Deposition of amyloid proteins in both the central and peripheral nervous systems lead to debilitating, and often deadly, organ dysfunction, including cerebral amyloid angiopathy, familial amyloid neuropathy, and Alzheimer’s disease (AD). Alzheimer’s disease is discussed in some detail in a separate chapter within this book, and therefore will not be discussed in detail in this chapter. In this chapter, we present the pathological mechanisms, disease manifestations, diagnostic approach, and treatment modalities for diseases of the nervous system caused by amyloid deposition. While significant strides have been made over the years in identifying key underlying pathologic mechanisms, the medical community’s understanding of these rare conditions remain limited. The primary goal of this chapter is to provide additional resources and information for clinicians to help identify these disorders early in their course before they cause irreparable damage to their patients.

Keywords: amyloid, neurology, familial amyloid neuropathy, cerebral amyloid neuropathy

1. Introduction

Cerebral amyloid angiopathy (CAA) is a disease of the small and medium vessels of the brain and the leptomeninges. Its hallmark pathological mechanism is the deposition of β-amyloid, a derivation of the amyloid precursor protein (APP), which leads to an array of clinical and radiologic findings. While the prevalence of CAA is challenging to quantify, in an autopsy study from the city of Vantaa, Finland, almost 70% of brain autopsy specimens from individuals aged 85 years or older showed some degree of cerebral amyloid deposition [1]. The most prevalent clinical finding is lobar intracerebral hemorrhage [2], which can be seen on gross specimen (Figure 1); other presentations can include transient neurologic symptoms, inflammatory leukoencephalopathy contributing to cognitive impairment, or incidental findings of microbleeds or hemosiderosis on MRI. Interestingly, the hallmark of Alzheimer’s disease (AD) is also an abnormal deposition of β-amyloid; however, these two diseases are distinctly different, both in the composition of the amyloid, and in the clinical neurologic manifestations.
1.1 Pathophysiology

The principal pathologic mechanism that is responsible for CAA is deposition of amyloid protein within the cerebral vasculature; specifically, β-amyloid protein deposition in the tunica media and the adventitia of cortical, subcortical, and leptomeningeal blood vessels. Amyloid can be viewed on histopathologic specimen with Congo Red stain (Figure 2). Subsequently, amyloid deposition causes necrosis, focal wall fragmentation and microaneurysms within the vessel walls [3]. These pathologic changes create an environment that leads to subsequent vessel leakage and even frank hemorrhage; these events can recur continuously throughout the course of the disease. The amyloid subtype is classified as β-amyloid, which is derived from the amyloid precursor protein (APP). APP is encoded on human chromosome 21, and is a membrane protein that is highly expressed at neuronal synapses. APP is cleaved by the enzymes beta secratase and gamma secratase to yield Aβ. The Aβ chains may then, in turn, misfold and polymerize, leading to amyloid formation and deposition. The complete mechanism of deposition is not fully understood, however, once deposited, the vasculature is prone to crack [3]. One possible model that has been proposed to promote amyloid deposition is that the mechanism is secondary to impaired clearance of Aβ amyloid through the perivascular drainage pathway [4]. While the APP has been implicated in both CAA and Alzheimer’s disease, the subsequent pathology and clinical manifestations diverge quickly based on which isoform of the Aβ amyloid is produced. In CAA, both Aβ 40 and Aβ 42 have been discovered in the walls of the vasculature, however, the Aβ 40 isoform predominates. In AD, Aβ 42 is found in the senile plaques that are histologically pathognomonic for the disease. Researchers also carefully analyzed cerebral
spinal fluid profiles and discovered that samples from CAA and AD patients were decreased in Aβ 40 and Aβ 42 respectively [5].

1.2 Genetics

Overall, CAA is a sporadic disease with no specific driver mutation identified to date; however, genetic susceptibilities have been identified that increase the risk of the disease [6]. Apolipoprotein E (APOE) is a plasma protein that is involved in cholesterol transport, and it exists in three different forms. Abnormalities in the APOE gene, also found to be linked to Alzheimer’s disease [7], are seen in some CAA patients; specifically, the e2 or e4 alleles have been found in approximately two thirds of patients with CAA [6]. Furthermore, a dose dependent relationship has been identified for the e2 allele [8]. Patients with the target alleles are at a higher likelihood for CAA related hemorrhage, earlier age of onset of disease, and greater risk for hemorrhage reoccurrence [9]. Ongoing research continues to work to uncover the specific mechanisms and the role of each allele; to date, the understanding is that the e4 allele increases the deposition of the amyloid [10], while the e2 allele changes the integrity of the cerebral vasculature, allowing for cracking and necrosis that predisposes to vessel rupture [10]. The e2 allele is also associated with larger intracerebral hemorrhages, increased mortality, and worse functional outcomes [11].

1.3 Intracerebral hemorrhage

The most prevalent clinical finding associated with CAA is acute intracerebral hemorrhage. Intracerebral hemorrhage secondary to CAA has characteristic imaging features. It is described as a lobar hemorrhage localized to the cortical and subcortical white matter within a hemispheric lobe of the brain (Figure 3). This is often compared with hypertensive hemorrhage that is often localized to the deeper structures of the brain, including yet not limited to, the basal ganglia and the putamen [12]. The lobar manifestation often mirrors the underlying distribution of the amyloid deposition, which has been shown to favor cortical vessels. Less commonly, cerebellar or subarachoid/subdural hemorrhage can be found, reflecting involvement of cerebellar or leptomeningeal vasculature [13]. Hemorrhages can occur in any lobe of the cerebrum, however, the lesions are most commonly localized to the posterior regions of the brain. This localization reflects the specific distribution of vascular amyloid deposition, particularly in the vessels of the temporal and occipital lobes [14]. While the direct mechanism and reason is unclear, this is most

Figure 3.
T1 weighted image demonstrating lobar hemorrhage secondary to amyloid angiopathy. Photograph courtesy of Roy Rhodes, MD, Professor of Pathology, Louisiana State University Health Sciences Center, New Orleans.
likely attributed to differences in tissue composition of the posterior vasculature that allows for easier deposition of amyloid [15]. When amyloid deposition occurs in the leptomeningeal vessels, the hemorrhage can extend beyond brain tissues into the subarachnoid and subdural spaces [16]. It should be noted that gradient-echo or susceptibility weighted sequence brain MRI can reveal cortical microbleeds, and this may be helpful in the diagnosis when identified; these findings are usually asymptomatic and can be found in the juxtacortical and cortical lobar regions, preferring the temporal and occipital lobes.

Similar to the presentation of acute ischemic stroke, the clinical signs and symptoms of intracerebral hemorrhage associated with CAA depend on the location and size of the lesion. Unfortunately, given the wide array of non-specific clinical symptoms, the accurate diagnosis of CAA remains incredibly challenging even for the most adept clinician. Currently, the only definitive diagnostic tool is a brain biopsy, which is rarely performed in vivo and often differed to autopsy. Clinicians can localize the site of the hemorrhage based on clinical presentation. Associated symptoms include headache, seizures, or changes in level of consciousness. The imaging revolution of the late twentieth century was instrumental in the development of the Boston Criteria, a validated set of criteria that has helped clinicians make the diagnosis of CAA using a combination of clinical signs and symptoms, and imaging features, or by pathologic specimen [17]. To date, the Boston Criteria is used as the primary foundation for research and treatment options for CAA; the criteria will be discussed further below.

1.3.1 Diagnosis

While our understanding of the disease process has significantly improved since it was first described, and even more so since imaging technology has evolved, the diagnosis of CAA still remains somewhat elusive. Similar to many other neurologic conditions, a definitive diagnosis can generally only be established post-mortem, based upon pathologic examination. The pathologist can view amyloid deposition on microscopic analysis, as well as see the hemorrhages on macroscopic examination. In clinical practice, clinical suspicion and MRI are the primary tools at the physician's disposal. CAA should be high on the differential diagnosis if MRI findings are positive for lobar hemorrhage without alternative explanation [17]. Advanced age will also support the diagnosis. Brain biopsy can be used; however, it is rarely performed in this setting.

The Boston Criteria, along with its updated modified version, is currently used to diagnose cerebral amyloid angiopathy. A recent paper by Greenberg and colleagues from the Massachusetts General Hospital details the evolution of the Boston Criteria [18]. The Boston Criteria were published initially in the year 1995. The authors stated that the key diagnostic category for the purpose of clinical care and for research is the category of "probable CAA", as this appeared to come closest to defining the disease short of tissue biopsy. In these cases of probable CAA, neuroimaging demonstrates multiple hemorrhages restricted to lobar regions of the brain. A modification to include blood or blood derivatives on imaging, in cortical sulci as one additional hemorrhagic lesion was added to the criteria in the year 2010. This addition is the basis for the "modified Boston Criteria". MRI of the brain is the essential tool for imaging in the Boston Criteria. The Boston Criteria has been validated through multiple studies, comparing it to the gold standards such as pathologic specimens [19].

1.3.2 Prognosis

Prognosis of intracerebral hemorrhage depends on several factors. Bleeds localized superficially will be less likely to cause any mass effects and will not impede
on the ventricles. Older patients with larger bleeds have less favorable outcomes. Overall, the mortality associated with intracerebral bleeds ranges from 10 to 30% [20]. Proper management can decrease the likelihood of hemorrhagic recurrence, however, it is not a guarantee. Patients with a prior ICH are 6 times as likely to have another event than those who have never had one [21].

1.4 Microbleeds and superficial siderosis

While intracerebral hemorrhage is the most common clinical and radiologic feature of CAA, there are other radiologic aspects of the disease that are important to mention, including microbleeds and cortical superficial siderosis. Both features are found incidentally on imaging. Microbleeds in the cortical areas are pathognomonic for CAA. They reflect tiny areas of hemosiderin deposition on gradient echo or other T2 weighted sequences that arise from small vessel disease and primarily appear in areas with significant amyloid deposition [22]. See Figure 4 for a radiographic image of the microbleeds.

The other incidental imaging finding associated with CAA is cortical superficial siderosis (cSS), defined as remote, chronic bleeding in cortical sulci. The finding is usually asymptomatic; however, it is a harbinger for higher risk of intracerebral hemorrhage [23]. It is a common finding in patients with CAA [24] and rarely found in patients with ICH unrelated to CAA [25]; the association ultimately led to the inclusion of cSS in the modified Boston criteria [24]. Unfortunately, it predicts poor functional outcome [26].

1.5 Transient focal neurologic episodes

An associated, albeit rare clinical feature of CAA are transient focal neurologic episodes (TFNE) [27]. These episodes are characterized as recurrent, brief episodes consisting of weakness, numbness, and paresthesias. In addition, patients describe that the symptoms spread over contiguous body parts. Most likely, TFNE represent deficiencies in the activity of cortical areas secondary to small hemorrhages. Given the non-specific nature of the symptomatology, the diagnosis and subsequent management of TFNE remains challenging. Key features that suggest TFNE as opposed to similar transient neurologic conditions such as migraines or seizure are
the recurrent nature that is localized to the site of prior lobar hemorrhage. Brain MRI with gradient echo can be used to identify convexity subarachnoid hemorrhage (cSAH), cSS, or CMBs in the cortical regions corresponding to TFNE symptoms. Interestingly, TFNEs are associated with cSS; in one study, CAA patients with TFNE were more likely to have cSS or cSAH than not [28]. In addition, tests to rule out other diagnoses can be considered in order to avoid misdiagnosis and subsequent inappropriate treatment. A case series of CAA patients with TFNE demonstrated that these patients have higher risks of intracerebral hemorrhage [29]. Proper diagnosis can avoid possible mistreatment with tPA for a presumed stroke which can increase the hemorrhagic burden of the disease.

1.6 Cerebral amyloid angiopathy related inflammation and beta-amyloid related angiitis

Cerebral amyloid angiopathy related inflammation (CAA-ri) and beta-amyloid related angiitis (ABRA) are distinct processes, but both are caused by an inflammatory response to Aβ amyloid deposition. Both processes present with a distinct clinical picture that is characterized as subacute and progressive [30]. Symptoms include cognitive decline, mental status changes, seizures, headaches, and focal neurologic deficits [31]. Interestingly, while both processes occur secondary to inflammation, the clinical course of ABRA is typically more insidious, possibly mirroring the findings of histopathologic exam. CAA-ri is associated with perivascular inflammation, while ABRA is described as transmural granulomatous inflammatory infiltrates, similar to what is observed in CNS vasculitis [32]. The rapid evolution of ABRA can lead to herniation if not identified and treated early [33]. While not as common as ICH, CAA-ri manifests earlier than the other findings of CAA [34]. Diagnostic criteria based on clinical and radiographic findings have been developed and validated for CAA-ri [34]. “Probably CAA-ri” is defined as having at least 1 typical clinical feature, asymmetric hyperintensities on T2-weighted MRI, previous evidence of CAA on susceptibility-weighted MRI, and absence of other causes. Definitive diagnosis can only be made on biopsy which would reveal confirmation of perivascular, transmural, or intramural inflammation along with amyloid deposition within the vasculature within the territory normally affected by CAA. These criteria were validated with a sensitivity of 82% and specificity of 97% in a clinical analysis [35]. Other laboratory findings include a normal ESR and CRP [34], and normal CSF analysis with pleocytosis and mildly elevated CSF protein [36]. A case report describes evidence of increased autoantibodies against amyloid in the CSF, pointing to a possible autoimmune response produced by the Aβ deposits [37]. Treatment involves the use of immunosuppression. Typical regimen involves a 5-day course of methylprednisolone followed by an oral steroid taper [38].

1.7 Cognitive impairment

Cognitive impairment has been associated with advanced CAA. In fact, on neuropsychological testing, most CAA patients demonstrate impairments of at least one domain [39]. A clinical-pathological study showed that moderate to severe CAA is associated with faster rates of cognitive decline [40]. The population-based Medical Research Council clinical-pathologic series found a odds ratio for dementia in CAA patients of 7.7 (95% CI, 3.3–20.4) [41]. As mentioned before, Aβ amyloid plays a role in the pathophysiology of Alzheimer’s disease, leading researchers to further analyze the connections between the two similar, albeit distinct pathologies. In one autopsy series, CAA was found in 26% of Alzheimer’s disease brains [42].
In addition, vascular disease may play a role in cognitive impairment in CAA. Studies demonstrate a correlation between the existence and prevalence of microbleeds and cognitive impairment suggesting that cerebral vascular disease may contribute to clinical neurologic dysfunction [43].

1.8 Management

Once diagnosed, the primary management goal of CAA is focused on prevention of recurrent hemorrhage. As mentioned before, studies revealed that patients with previous hemorrhage are at increased risk of recurrent hemorrhage, and as the number of incident hemorrhages increase, the risk of a subsequent event also increases. A thorough medicine reconciliation is imperative to assess the needs of the patient given any comorbid conditions and medication risks.

1.8.1 Anticoagulation and antiplatelet therapy

The evaluation of anticoagulative and antiplatelet agents is crucial to assess risk of future hemorrhages and needs to be individualized for each patient. Initial assessment of the patient should include factors such as prior intracerebral hemorrhage, presence of other imaging findings, class of antithrombotic agent being used (warfarin, DOACs, ASA, etc.), and the duration of treatment. Patients who are at high risk for thromboembolic events (e.g. cancer patients, patients with underlying hypercoagulable conditions, mechanical heart valves, etc.) might need treatment in order to prevent thrombotic, and subsequent ischemic, events. In addition, atherosclerotic disease and atrial fibrillation need to be managed appropriately in order to decrease risks of thrombosis. New onset ischemic stroke, pulmonary embolism, and myocardial infarction need to be managed with considerable care since intravenous thrombolysis is contraindicated in the setting of intracerebral hemorrhage [44]. In certain cases, endovascular repair and mechanical thrombectomy can be used in lieu of tPA.

1.8.2 Anti-hypertensives

While hypertensive strokes are usually associated with small vessel disease of the inner brain areas, special attention needs to be placed on blood pressure management. The PROGRESS Trial examined the effects of perindopril-based lowering of blood pressure on the evolution of intracerebral hemorrhage (ICH) in the setting of clinically defined CAA [45]. In this multicenter, randomized, placebo-controlled trial, 6105 patients with cerebrovascular disease were assigned to blood pressure reduction using either perindopril, and in some cases together with indapamide, or placebo. Outcomes were assessed as either: probable CAA related ICH as defined by the Boston Criteria, probable hypertension related ICH, and unclassified ICH. With a median follow up of 3.9 years at the time of publication, the authors reported 16 cases of probable CAA-related ICH, 51 probable hypertension related ICH, and 44 unclassified cases of ICH. Active treatment reduced the risk of CAA-related ICH by 77% in this study. The authors concluded that therapy to lower blood pressure is of value in providing some degree of protection against ICH in CAA. A subset analysis of the PROGRESS trial showed that patients with probable CAA and ICH had fewer hemorrhagic recurrences if their blood pressure was tightly controlled on perindopril [46]. Furthermore, an observational cohort study of patients with known ICH continued to have higher risks of recurrent lobar hemorrhage if their blood pressure was inadequately controlled [47].
1.8.3 Statins

The role of statin therapy in the management of CAA and potential or recurrent ICH seems paradoxical given the current understanding of the role of statins in preventing vascular events. The SPARCL trial showed an increased incidence of ICH in the statin arm compared to placebo. Given these results, the trial investigators recommended that perhaps statins should be avoided in patients with a history of ICH [48]. In addition, retrospective analysis of patients with ICH treated with statins showed increased incidence of microbleeds, particularly in cortex and subcortex [49]. Current recommendations are to avoid statins in survivors of ICH [50], however, further investigations revealed that use of statins prior to ICH was associated with reduced mortality and disability at 90 days [51]. In addition, a meta-analysis showed no increase in ICH in patients taking a statin once they developed radiologic evidence of ICH [52].

2. Familial amyloid polyneuropathy

Familial amyloid polyneuropathy (FAP) represents a group of multisystem, life-threatening disorders characterized by the deposition of amyloid protein in either the peripheral motor nervous system, the sensory system, or the autonomic nervous systems, or in a combination of these subsets of the nervous system. These disorders are hereditary forms of amyloidosis, which are typically inherited in an autosomal dominant manner [53]. FAP was first described by Andrade in north Portugal in 1952 [54], and subsequently was described in Japan [55] and Sweden [56]. To date, three main proteins are implicated in the pathogenesis of the majority of cases of FAP: transthyretin, apolipoprotein A-1, and gelsolin. The extent of neurological and non-neurologic organ system involvement is variable, depending on the precursor protein, making the diagnosis often quite challenging. Early and accurate diagnosis is necessary to guide further testing, and subsequent treatment options, and could also contribute to improved research strategies to augment understanding of the pathophysiology and improve therapy.

2.1 ATTR amyloidosis

The most common type of familial amyloid polyneuropathy is caused by the misfolding of transthyretin. Transthyretin, the gene for which is located on human chromosome 18 [57], is produced in the liver, and under normal physiologic conditions, it is responsible for the transport of thyroxin as well as binding of retinol. Due to the electrophoretic mobility of transthyretin, it was originally named prealbumin. While researchers have identified many mutations responsible for the development of amyloid secondary to transthyretin, the substitution for methionine for valine at position 30 of the transthyretin gene is the most common mutation [58]. However, despite the simple missense mutation, disease phenotype is widely variable in severity, symptomatology, and age of onset [59].

2.2 Additional mutations causing FAP

Mutations in the apolipoprotein A1 (APOA1), a protein that is synthesized mainly in the small intestine and liver, is also associated with FAP. It was first described by van Allen in Iowa [60]. While at least 16 mutations have been identified in the APOA1 gene that are associated with amyloidosis [61], neuropathic symptoms are only associated with the Gly26arg mutation [62]. Similar to FAP
caused by TTR, APOA1 amyloid also causes a length-dependent polyneuropathy; however, polyneuropathy is not the primary feature of this disease. Renal, hepatic, and gastrointestinal symptoms are the most frequently documented symptoms. Treatment is mainly supportive at present, and is geared toward relief of symptoms. Hepatorenal transplantation for end stage renal disease has been associated with a decrease in concentration of plasma amyloidogenic proteins along with improvement of neuropathic symptoms [63].

Gelsolin-related FAP was first described in Finland in 1969, and it is referred to as the Finish type of amyloidosis [64]. The gelsolin gene is located on chromosome 9, and is a protein that normally binds to actin, and regulates the assembly and disassembly of filaments. Mutations in the gene increase the rate of gelsolin cleavage and cause amyloidosis [65]. Gelsolin amyloid is characterized by the triad of cranial neuropathies, corneal lattice dystrophy, and cutis laxa [66]. Amyloid deposition in gelsolin-related FAP affects the upper branch of the facial nerve, leading to bilateral facial paresis and reduced facial expressions; there is also involvement of the hypoglossal, glossopharyngeal, and vagus nerves. Patients typically begin to complain initially of symptoms of sensory neuropathy around the 5th and 6th decade of life, in a distribution which affects the lower extremities. In addition, there are reports of autonomic involvement in this variant of FAP [67]. Amyloid deposition can also affect the central nervous system in gelsolin-related FAP: gelsolin amyloid can cause an angiopathy leading to vascular malformations in the brain and spinal cord [68]. To date, no specific treatment has been developed for gelsolin amyloidosis. Management is currently focused on proper ophthalmologic care, and plastic surgery for facial laxity [69].

2.3 Signs and symptoms

One of the key features of FAP that distinguishes it from other neuropathy presentations is that it typically involves multiple areas of the nervous system, with focal neuropathies, sensorimotor polyneuropathies, and autonomic neuropathies. The most recognized manifestation of focal neuropathy is carpal tunnel syndrome, which occurs secondary to endoneurial amyloid deposits of the median nerve [70]. Similar to idiopathic carpal tunnel syndrome, patients usually experience paresthesias in the thumbs and the second and third digits of the hands, along with significant wrist pain. The symptoms experienced with FAP are usually significantly more severe than in idiopathic carpal tunnel syndrome [70]. The sensorimotor neuropathy of FAP is a length dependent neuropathy that affects the small myelinated and unmyelinated fibers first [71]. Patients will initially describe symptoms of foot discomfort, characterized as numbness, paresthesias, and allodynia. On neurologic exam, patients will have decreased pin prick and impaired thermal sensation. With disease onset, light touch, proprioception, motor strength and reflex will be primarily preserved, however, as the disease progresses and affects larger sensory and motor nerve fibers, patients will begin to note deficit changes in these areas as well. Patients will, over time, exhibit significant weakness in their hands and feet, decreased or absent ankle reflexes, and diminished vibration and proprioception in the distal distributions of the nerves. The disease will continue to travel proximally, involving the proximal lower extremities, truck, and the upper extremities. Patients then will begin to have difficulty with ambulation, secondary to their loss of muscle strength and proprioception. Patients will then often start to develop joint deformities (e.g. Charcot joints) as well as planar ulcers, because of the lack of sensation in their feet [58].

Patients with FAP show significant autonomic dysfunctions as well, particularly with the early age onset form. Typical sequelae of autonomic dysfunction affecting the cardiovascular, genitourinary, and gastrointestinal systems will be present.
Patients will exhibit signs and symptoms of orthostatic hypotension, including light headedness, dizziness, fatigue, and blurry vision upon standing. Patients often develop postprandial diarrhea and/or constipation, as well as post-prandial vomiting due to gastroparesis. In particular, the autonomic control of the cardiovascular, genitourinary, and gastrointestinal systems are affected. With regard to the genitourinary system, symptoms may include urinary retention and incontinence, as well as sexual dysfunction. However, it is important to note that FAP is not associated with central nervous system involvement [58].

2.4 Pathophysiology

The key pathologic step in the development of FAP is the misfolding of the transthyretin protein, which leads to pathologic deposition within the nervous system. Under normal physiologic conditions, TTR is a tetrameric protein with surface receptors that bind retinol and thyroxine, and then carries these in the circulation [72]. TTR is mainly produced in the liver, but also in the retinal pigment epithelium of the eyes and choroid plexus [73]. There are also reports of TTR synthesis in the neurons [74] and peripheral nerve Schwann cells [75]. Upon pathologic misfolding, ATTR deposits unevenly throughout the nervous system. As the ATTR accumulates, it causes pathology through damage to the nerves by mechanical compression, blood vessel invasion, and the toxicity of fibrils to normal cellular and organ structures [58]. Although many mutations have been identified in the TTR gene in patients with ATTR amyloidosis, there are also many cases with so-called wild-type ATTR amyloidosis. In these latter cases, there is abnormal folding of the TTR peptides, but no mutation identified. The molecular pathophysiology in these cases remains to be fully elucidated.

2.5 Diagnosis

The diagnosis of FAP can be elusive, considering the relatively low incidence and the non-specific constellation of symptoms. In fact, the differential diagnosis of polyneuropathy is quite wide (see Table 1). As always, a thorough history can potentially help tease out the diagnosis. In endemic areas, a family history can help make the diagnosis more straightforward, when taken together with the constellation of clinical involvement by signs and symptoms. Molecular diagnostics—that is, DNA sequencing, either by rapid allele specific oligonucleotide nucleic acid amplification, or by actual sequencing, will help secure the diagnosis. However, the diagnosis can be quite challenging in patients without a family history of FAP. In sporadic cases, keys to the proper diagnosis include the progressive nature of the disease affecting autonomic, sensory, and motor components of the nervous system, in addition to involvement of other organs affected by amyloid deposition (e.g. cardiac involvement, carpal tunnel syndrome). Since neuropathy is often one of the initial presenting symptoms, it is important that clinicians rule out some of the more common causes of neuropathy first. A useful adjunct to diagnosis, typically done prior to molecular diagnostic studies, is Nerve Conduction Velocity (NCV) studies and electromyography, which will document the specific areas of and electrical features of the neuropathy. Formal autonomic nervous system, including Quantitative Sudomotor Axon Reflex Testing (QSART) will document the extent of dysautonomia. These are typically not specific for FAP, however. Biopsy of a peripheral nerve may demonstrate amyloid, and analysis of the amyloid material in the biopsy by High Performance Liquid Chromatography and Mass Spectroscopy may confirm the amyloid as being composed of ATTR. This is definitive for a diagnosis of FAP, and in such a case, molecular diagnostics are an adjunct that will
allow testing of family members. However, nerve biopsy is invasive, and does carry the risk of causing neurologic damage itself.

2.6 Treatment

The treatment of FAP has progressed significantly over the years since the first cases were reported. The changes in disease therapy are a reflection of developments in the understanding of the disease pathobiology, as well as the advancements in medical treatment overall. The approach to treatment is divided into interventions for symptomatic relief, on the one hand, and disease modifying agents on the other hand. Common anticonvulsants such as gabapentin and pregabalin [76] are used to ameliorate symptoms, as well as antidepressants such as the tricyclic antidepressants (TCAs) [77] and serotonin-norepinephrine reuptake inhibitors (SNRI) [78]. TCAs are particularly helpful in patients who have significant night-time symptoms, given their sedatives properties; however, considerable attention is warranted for exacerbation of autonomic dysfunction. Duloxetine is the most widely used, and studied, SNRI for the treatment of FAP.

2.6.1 Liver transplantation

Liver transplantation has been a treatment option for management of FAP for several decades, based on the understanding that replacing a liver producing defective
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TTR with a liver that makes normal TTR protein will improve the long-term outcome. As an example of the results of liver transplantation in this setting, Yamashita and colleagues from Kumamoto University hospital reported on a cohort 80 patients with FAP due to the mutation Val30Met, managed between January 1990 and December 2010. The transplant group consisted of 37 patients who had a partial hepatic graft via living donor transplantation in Japan or who underwent liver transplantation in Sweden, Australia, or the United States. The non-transplant group consisted of 43 patients with FAP. The transplant group had prolonged survival (p < 0.001) compared with the non-transplant group. The estimated probability of survival at 10 years was 56.1% for the non-transplant group vs. 100% for the transplant group [79].

2.6.2 Disease modifying agents

The first development in disease modifying agents for FAP occurred with the repurposing of the non-steroidal anti-inflammatory medicine diflusinil. Although liver transplantation has proved to be a successful treatment option, there are many barriers to its use, including availability of technical expertise, availability of a donor, co-morbidities in the patient, and cost. Pre-clinical investigation showed that diflusinil can bind to the thyroxine binding site of the TTR tetramer, and stabilize TTR in the tetramer form, thus preventing the TTR protein subunits from misfolding and being deposited as amyloid. A multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial demonstrated that the use of diflunisal reduces the rate of progression of neurologic impairment [80].

Tafamidis, a thyroxine analogue, is a disease-modifying agent approved for use in the treatment of FAP. Just as diflusinil can stabilize TTR tetramers, it was hypothesized that a synthetic thyroxine analogue may be able to bind to the thyroxin-binding sites on the TTR protein and stabilize the TTR tetramers, similarly preventing them from disassociating, misfolding, and forming amyloid fibrils [81]. A phase III clinical trial in patients with Val30Met ATTR amyloidosis documented delayed progression of neuropathic symptoms with use of Tafamidis, as compared to placebo [82]. An extension study also showed slowing of neuropathy progression [83]. Interestingly, in addition to slowing down the progression of amyloid neuropathy, Tafamidis has also proved effective in improving outcome in ATTR amyloid cardiomyopathy [84].

2.6.3 Gene expression modifying therapy

While stabilization of the TTR tetramer has proved to be somewhat effective in slowing progression of disease, there has, in recent decades, been an active effort to develop genetic modifying therapy in ATTR amyloidosis. Two gene-silencing treatments, Patisiran and Inotersen have been developed and are FDA approved. Patisiran, a small interfering RNA molecule, is delivered parenterally and reduces TTR production [85]. A phase III trial tested Patisiran against placebo; all endpoints were met, including a decrease in neuropathic symptoms and increase in quality of life [86]. Inotersen, an antisense oligonucleotide, was also designed to reduce the production of TTR. A randomized phase III clinical trial in ATTR amyloidosis patients demonstrated a statistically significant decrease in neuropathic impairment [87]. True gene therapy remains to be established for ATTR amyloidosis.

3. Conclusion

Given the constellation of non-specific symptoms, the diagnosis of Cerebral Amyloid Angiopathy and Familial Amyloid Polyneuropathy remains challenging,
even to the most adept physician. Despite these challenges, the medical and scientific community’s understanding of the diseases has grown considerably since the diseases were first identified and continues to grow, reflected by the increasing number of articles published on the topics. As our knowledge base continues to expand, not only has our ability to make more accurate and timely diagnoses grown stronger, but our treatment and management options have increased as well. It is the authors’ hope that the reader has gained a deeper appreciation for the role of amyloid in pathology of the neurologic system and that it will help improve the lives of their patients.

4. Methodology

The information presented in each of the former sections was culled from a literature search using the National Library of Medicine, PubMed website, using key search terms. This involved the search terms amyloidosis, cerebral amyloid angiopathy, and familial amyloid polyneuropathy. From the articles culled, those published in peer reviewed journals were selected for inclusion, most prominently describing initial observations and key clinical trials that advanced therapies.
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