Ultrastructure in Transthyretin Amyloidosis

Subjects: Medicine, General & Internal

Contributor: Haruki Koike

Transthyretin (TTR) amyloidosis is caused by systemic deposition of wild-type or variant amyloidogenic TTR (ATTRwt and ATTRv, respectively). ATTRwt amyloidosis has traditionally been termed senile systemic amyloidosis, while ATTRv amyloidosis has been called familial amyloid polyneuropathy. Although ATTRwt amyloidosis has classically been regarded as one of the causes of cardiomyopathy occurring in the elderly population, recent developments in diagnostic techniques have significantly expanded the concept of this disease. For example, this disease is now considered an important cause of carpal tunnel syndrome in the elderly population. The phenotypes of ATTRv amyloidosis also vary depending on the mutation and age of onset. Peripheral neuropathy usually predominates in patients from the conventional endemic foci, while cardiomyopathy or oculoleptomeningeal involvement may also become major problems in other patients. Electron microscopic studies indicate that the direct impact of amyloid fibrils on surrounding tissues leads to organ damage, whereas accumulating evidence suggests that nonfibrillar TTR, such as oligomeric TTR, is toxic, inducing neurodegeneration. Microangiopathy has been suggested to act as an initial lesion, increasing the leakage of circulating TTR. Regarding treatments, the efficacy of liver transplantation has been established for ATTRv amyloidosis patients, particularly patients with early-onset amyloidosis. Recent phase III clinical trials have shown the efficacy of TTR stabilizers, such as tafamidis and diflunisal, for both ATTRwt and ATTRv amyloidosis patients.

Keywords: angiopathy ; diflunisal ; electron microscopy ; oligomers ; pathogenesis ; pathology ; protein misfolding disease ; Schwann cell ; tafamidis ; therapy

1. Introduction

Transthyretin (TTR) amyloidosis is caused by systemic deposition of wild-type or variant amyloidogenic TTR (ATTRwt and ATTRv, respectively). ATTRwt amyloidosis has been traditionally named senile systemic amyloidosis because postmortem studies revealed that its prevalence becomes higher as age at examination increases [1]. On the other hand, ATTRv amyloidosis has been called familial amyloid polyneuropathy [2][3][4][5]. Although this disease was originally reported in geographically restricted areas (i.e., endemic foci) of Portugal, Japan, and Sweden [6][7][8], its global prevalence has been demonstrated [2][9]. The Val30Met mutation, alternatively called p.Val50Met according to the Human Genome Variation Society nomenclature, has been considered the most common mutation because patients from endemic foci and many of the late-onset (more than 50 years of age) patients from nonendemic areas have this mutation [2][10]. However, recent progress in diagnostic techniques has increased the number of newly diagnosed patients with non-Val30Met mutations [11]. Over 130 mutations have been reported so far [12], and certain types of non-Val30Met patients are more frequent than Val30Met patients in some countries [13][14][15].

Regarding the treatment for ATTR amyloidosis, the efficacy of liver transplantation, which is usually indicated for early-onset ATTRv amyloidosis patients, has been established since the 1990s [16][17]. Recent phase III clinical trials have shown the efficacy of TTR stabilizers for both ATTRwt and ATTRv amyloidosis patients [18][19][20]. In addition, gene-silencing drugs that significantly reduce the amount of TTR produced in the liver have also become available for ATTRv amyloidosis [21][22]. Eliminating causative proteins is more reasonable than merely stabilizing the protein because nonfibrillar TTR may also exert harmful effects, as described later.

2. Diversity of Clinical Features

As ATTR amyloidosis is a systemic disease, patients exhibit variable clinical features depending on the site of amyloid deposition [23]. ATTRwt amyloidosis has classically been regarded as one of the causes of cardiomyopathy in the elderly population. Studies of autopsy specimens revealed that a significant proportion of the elderly population have wild-type TTR deposition, particularly in the heart (12 to 25% of subjects aged >80 years), despite a lack of relevant symptoms [24][25][26]. However, the recent development of diagnostic techniques for amyloidosis has significantly expanded the concept of this disease [27]. For example, this disease is now considered an important cause of carpal tunnel syndrome in the

elderly population [27][28]. Some studies have also suggested an association between wild-type TTR deposition in ligaments and spinal canal stenosis [27][29][30].

The phenotypes of ATTRv amyloidosis are also variable, depending on the mutation and age at onset [2][12]. As the classical name “familial amyloid polyneuropathy” indicates, peripheral neuropathy usually predominates in patients with conventional endemic foci [31][32]. Cardiomyopathy or oculoleptomeningeal involvement may also become major problems in others, particularly in patients with non-Val30Met mutations [12][33]. For example, Val112Ile and Thr60Ala mutations are usually associated with cardiac amyloidosis, while Tyr114Cys mutation causes oculoleptomeningeal amyloidosis [12]. Regarding the most common mutation, Val30Met (i.e., ATTR Val30Met amyloidosis), patients from the conventional endemic foci of Portugal and Japan exhibit textbook features of amyloid neuropathy, such as the following: early disease onset ranging in age from the late 20s to early 40s; a high penetrance rate; a nearly 1-to-1 male-to-female ratio; marked autonomic dysfunction; loss of superficial sensation, including nociception and thermal sensation (i.e., sensory dissociation); atrioventricular conduction block requiring pacemaker implantation; and the presence of anticipation of age at onset (**Table 1**) [2][34][35][36]. By contrast, patients with Val30Met mutations from nonendemic areas exhibit an older age at disease onset of over 50 years, a low penetrance rate, extreme male preponderance, relatively mild autonomic dysfunction, loss of all sensory modalities rather than sensory dissociation, the frequent presence of cardiomegaly, and the absence of anticipation of age at onset [2][10][37][38][39]. Despite the presence of the same mutation in the *TTR* gene, the reason for the differential clinical features between early- and late-onset cases has not been clarified.

Table 1. Comparison of the two major forms of hereditary transthyretin Val30Met amyloidosis *.

Features	Early-Onset Patients from Endemic Foci	Late-Onset Patients from Nonendemic Areas
Age of onset	**Late 20s to early 40s**	**≥50 years**
Sex	**Male = female**	**Male > female**
Family history	**Common**	**Frequently absent**
Penetrance rate	**High**	**Low**
Cardiac involvement	**Conduction defects**	**Heart failure**
Sensory dissociation	**Common**	**Rare**
Autonomic dysfunction in early disease stage	**Severe**	**Mild**
Modality of nerve fiber loss	**Small > large**	**Small = large**
Amount of amyloid deposits in the peripheral nervous system	**Large**	**Small**
Length of amyloid fibrils	**Long**	**Short**

* Based on previous reports [2][23][40].

3. Characteristics of Amyloid Fibrils Determining the Clinicopathological Features

Previous studies have demonstrated differences in the characteristics of amyloid fibrils depending on the age of onset and the type of mutation in patients with ATTRv amyloidosis [40][41][42][43][44]. In early-onset Val30Met cases, long and thick amyloid fibrils are common (**Figure 2**A), whereas the fibrils are usually short and thin in late-onset Val30Met cases and most non-Val30Met cases (**Figure 2**B) [40][42][44]. In addition, amyloid deposits in early-onset Val30Met cases tend to be highly congophilic and show strong apple-green birefringence, while those in late-onset Val30Met cases are generally weakly congophilic and show faint apple-green birefringence (**Figure 1**) [43]. These differences in the characteristics of amyloid deposits between early- and late-onset cases are particularly conspicuous in the heart [41][43]. Interestingly, short amyloid fibrils and a weak affinity of amyloid deposits for Congo red have also been reported for cardiac amyloid deposits in patients with ATTRwt amyloidosis [45]. A study of autopsied Japanese Val30Met patients demonstrated that most TTR in cardiac amyloid deposits from the early-onset cases was variant TTR, whereas wild-type TTR constituted more than half of the TTR in the deposits from the late-onset cases [43]. In ATTRv amyloidosis patients who undergo liver transplantation, cardiac amyloidosis may progress even after transplantation due to wild-type TTR deposition, particularly in elderly male patients [46][47]. These findings suggest that the mechanism of amyloid deposition in the heart is similar between late-onset

ATTRv amyloidosis patients and ATTRwt amyloidosis patients. Interestingly, ATTRwt amyloidosis mainly affects males, who account for approximately 90% of patients [27][28]. This male preponderance is in accordance with late-onset ATTR Val30Met amyloidosis cases [10], but not with early-onset Val30Met cases, which show a nearly 1-to-1 male-to-female ratio [31].

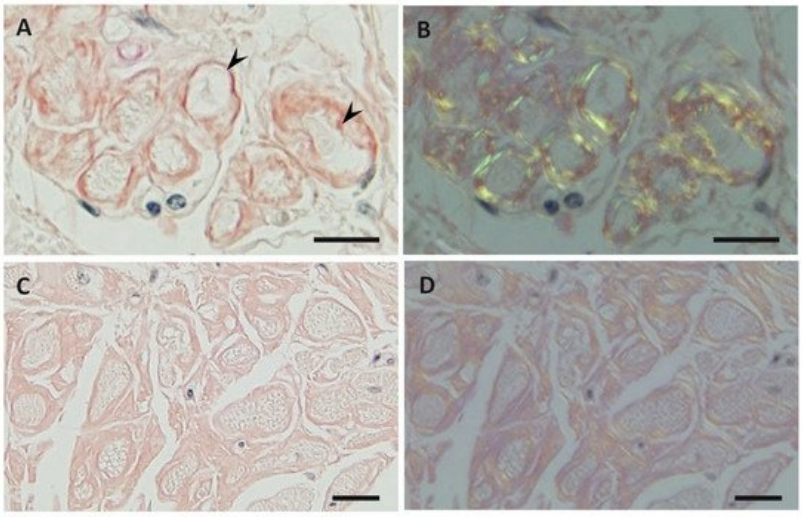

Figure 1. Representative photographs of cardiac amyloid deposits in early-onset ATTR Val30Met amyloidosis patients from endemic foci (**A**,**B**) and late-onset ATTR Val30Met amyloidosis patients from nonendemic areas (**C**,**D**) obtained at autopsy. Alkaline Congo red staining. In early-onset patients from endemic foci, the amyloid deposits tend to be highly congophilic (**A**) and show strong apple-green birefringence (**B**). In addition, amyloid deposits tend to induce atrophy and degeneration of myocardial cells, particularly in the subendocardial layer, producing a histologic picture of amyloid rings (arrowheads). In late-onset patients from nonendemic areas, the amyloid deposits are generally weakly congophilic (**C**) and show faint apple-green birefringence (**D**). Atrophy or degeneration of myocardial cells is not conspicuous in late-onset patients from nonendemic areas compared to early-onset patients from endemic foci. Scale bars = 20 μm.

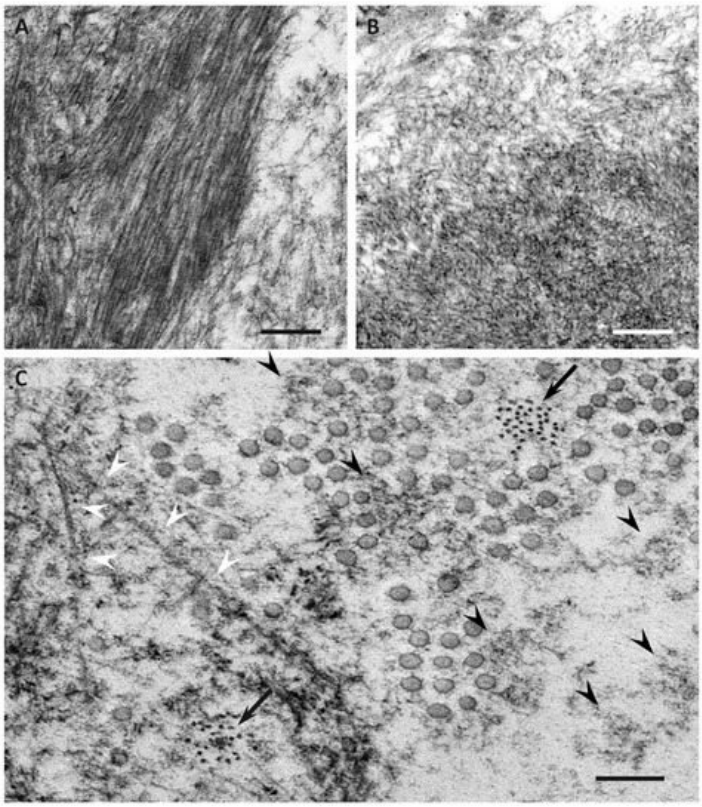

Figure 2. Representative electron microscopic photographs of amyloid fibrils in early-onset ATTR Val30Met amyloidosis patients from endemic foci (**A**,**C**) and late-onset ATTR Val30Met amyloidosis patients from nonendemic areas (**B**). Cross sections of sural nerve biopsy specimens. Uranyl acetate and lead citrate staining. Amyloid fibrils tend to be long and thick in early-onset patients from endemic foci (**A**), whereas those in late-onset patients from nonendemic areas are generally short and thin (**B**). Dotty structures (arrows) are frequently observed among amorphous electron-dense extracellular

materials (black arrowheads) (**C**). Elongated, mature amyloid fibrils are also observed (white arrowheads). Circular structures with a diameter of 50 to 70 nm are collagen fibers. Scale bars = 0.2 μm.

An important issue tightly related to the contribution of wild-type TTR to the mechanisms of amyloid fibril formation is the truncation of TTR by proteases, such as trypsin and plasmin [48][49]. A large amount of C-terminal fragments of TTR, starting at positions around amino acid 50, have been found in the amyloid deposits of late-onset ATTR Val30Met amyloidosis cases and most ATTRv amyloidosis cases with non-Val30Met mutations, whereas N-terminal fragments are present in only small amounts [41][42][50]. C-terminal fragments are also present in the amyloid deposits of ATTRwt amyloidosis cases [45][50]. By contrast, amyloid deposits consist mainly of full-length TTR in early-onset Val30Met patients [41][50]. Importantly, truncated TTR resulting from proteolytic cleavage was shown in vitro to remain associated with the tetramer and was released only under certain circumstances, such as shear stress [51]. As organs liable to receive shear stress, such as the heart, ligaments, and tendons, tend to have amyloid deposits resulting from wild-type TTR deposition in elderly patients [52], TTR truncation may determine the sites of amyloid deposition, particularly in elderly patients.

4. Impact of Amyloid Fibril Formation on Neighboring Tissues

Electron microscopic studies of nerve biopsy specimens from patients with ATTRv amyloidosis have shown that amyloid fibrils were formed among amorphous electron-dense materials located in extracellular spaces of the endoneurium [44]. Amorphous electron-dense materials tend to be observed around microvessels and the subperineurial space. Among these amorphous materials, dotty or fine fibrillar structures are frequently observed (**Figure 2**C). The dotty structures seem to be the core of amyloid fibrils because slightly elongated fibrillar structures with a thickness similar to the diameter of these dots are frequently found [44]. The mature long fibers usually occupy the central part of the large aggregations of amyloid fibrils, while the amorphous materials, dotty structures, and short amyloid fibrils tend to be present at the periphery of the aggregates of amyloid fibrils. During the process of amyloid fibril maturation, amyloid fibrils seem to pull surrounding tissues [44]. This traction of neighboring tissues seems to be conspicuous in cases with long and thick amyloid fibrils, such as early-onset Val30Met cases in endemic foci (**Figure 3**A) [40][44]. By contrast, amyloid fibril maturation seems to have a smaller influence on neighboring tissues in cases with short and fine amyloid fibrils, such as late-onset Val30Met cases in nonendemic areas (**Figure 3**B) [40][44].

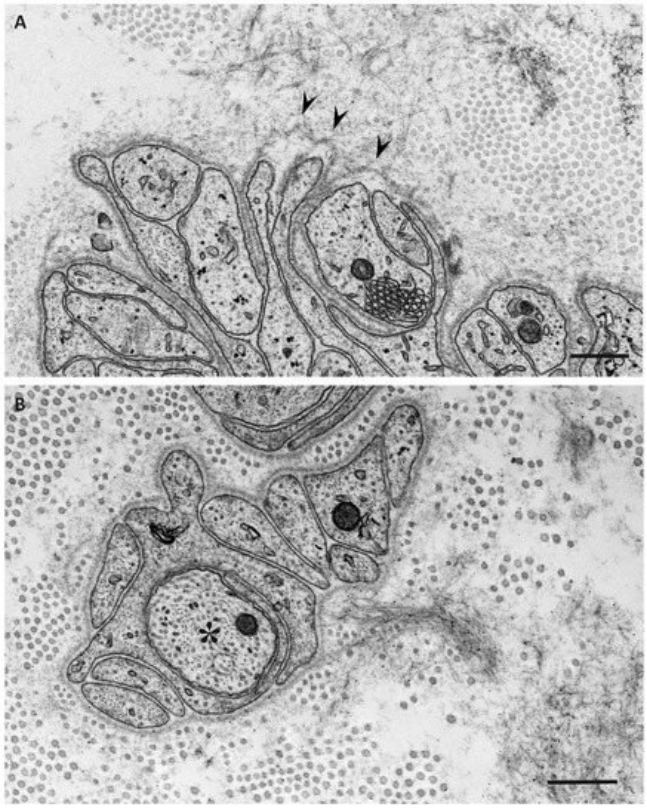

Figure 3. Impact of amyloid fibril formation on neighboring tissues in early-onset ATTR Val30Met amyloidosis patients from endemic foci (**A**) and late-onset ATTR Val30Met amyloidosis patients from nonendemic areas (**B**). Cross sections of sural nerve biopsy specimens. Uranyl acetate and lead citrate staining. During the process of amyloid fibril maturation, amyloid fibrils seem to pull surrounding tissues. This traction of neighboring tissues seems to be conspicuous in patients with long and thick amyloid fibrils, such as early-onset Val30Met patients from endemic foci (**A**). By contrast, the impact of amyloid fibril maturation on neighboring tissues seems to be less in patients with short and fine amyloid fibrils, such as

late-onset Val30Met patients from nonendemic areas (**B**). The stretched basement membrane in (**A**) is indicated by arrowheads. An unmyelinated fiber in (**B**) is indicated by an asterisk. Scale bars = 0.5 µm.

As a result, Schwann cells adjacent to amyloid fibril masses become atrophic and distorted, particularly in early-onset patients with long and thick amyloid fibrils (**Figure 4**) [40][44]. Small-diameter nerve fibers, particularly unmyelinated fibers, seem to be liable to this direct insult resulting from amyloid fibril formation. In contrast, myelinated fibers, particularly large myelinated fibers, seem to be resistant to such stress because the contact between these fibers and amyloid fibril aggregates is usually partial, even though the contact does occur. In addition, the basement and cytoplasmic membranes of Schwann cells that are apposed to amyloid fibrils, particularly long fibrils, tend to become indistinct, suggesting the direct damage of Schwann cells by amyloid fibril invasion [40][44]. An affinity of amyloid fibrils for Schwann cell membranes mediated by their common constituents may participate in this process [53]. A previous study suggested that TTR binds to the plasma membrane and exerts toxic effects by altering membrane fluidity [54].

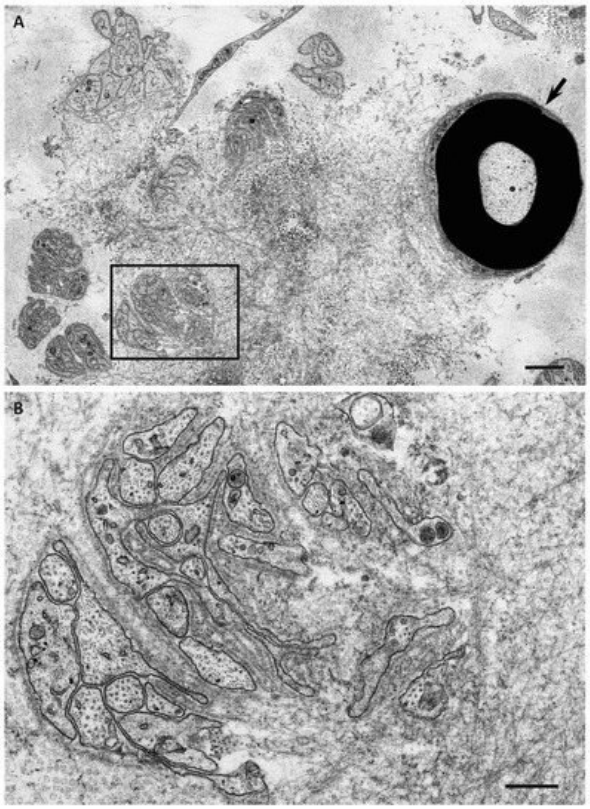

Figure 4. Aggregation of amyloid fibrils and Schwann cells in ATTRv amyloidosis. A cross section of sural nerve biopsy specimen from an early-onset Val30Met patient from an endemic focus. Uranyl acetate and lead citrate staining. Schwann cells associated with unmyelinated fibers that are apposed to amyloid fibrils become atrophic and distorted, whereas myelinated fibers, particularly large myelinated fibers (arrow), tend to be preserved because the apposition of these fibers to amyloid fibril aggregates is usually partial. A high-powered view of representative Schwann cells associated with unmyelinated fibers in the box in (**A**) is shown in (**B**). Scale bars = 2 µm (**A**) and 0.5 µm (**B**).

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