Familial amyloid polyneuropathy

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Lancet Neurol 2011; 10: 1086–97

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Familial amyloid polyneuropathies (FAPs) are a group of life-threatening multisystem disorders transmitted as an autosomal dominant trait. Nerve lesions are induced by deposits of amyloid fibrils, most commonly due to mutated transthyretin (TTR). Less often the precursor of amyloidosis is mutant apolipoprotein A-1 or gelsolin. The first identified cause of FAP—the TTR Val30Met mutation—is still the most common of more than 100 amyloidogenic point mutations identified worldwide. The penetrance and age at onset of FAP among people carrying the same mutation vary between countries. The symptomatology and clinical course of FAP can be highly variable. TTR FAP typically causes a nerve length-dependent polyneuropathy that starts in the feet with loss of temperature and pain sensations, along with life-threatening autonomic dysfunction leading to cachexia and death within 10 years on average. TTR is synthesised mainly in the liver, and liver transplantation seems to have a favourable effect on the course of neuropathy, but not on cardiac or eye lesions. Oral administration of tafamidis meglumine, which prevents misfolding and deposition of mutated TTR, is under evaluation in patients with TTR FAP. In future, patients with FAP might benefit from gene therapy; however, genetic counselling is recommended for the prevention of all types of FAP.

Introduction

Amyloidoses are a group of diseases characterised by tissue deposition of insoluble proteins and fibril aggregates oriented in a β-pleated sheet structure that form unbranched amyloid fibrils of 10–12 nm diameter. Amyloidosis can be acquired or hereditary. There are three main types of familial amyloid polyneuropathy (FAP), defined according to the precursor protein of amyloid: transthyretin (TTR), apolipoprotein A-1, and gelsolin. The main features of each type of FAP, and current approaches to diagnosis and treatment, are shown in the table.

TTR FAP is a life-threatening disease transmitted as an autosomal dominant trait. Nerve lesions are induced by deposits of fibril protein caused by mutated TTR (mTTR). TTR FAP typically causes a nerve length-dependent polyneuropathy that starts in the feet with loss of temperature and pain sensations, with autonomic dysfunction leading to death within 10 years on average. Apoliprotein A-1 amyloidosis, also known as the Iowa type, is characterised by the deposition of amyloid in major organs, including the kidneys, liver, and heart. Although a nerve length-dependent polyneuropathy can occur in apolipoprotein A-1 FAP, it is not a prominent feature of the disease. Gelsolin amyloidosis is characterised by cranial and peripheral sensory neuropathy, corneal lattice dystrophy, and cutis laxa. The course of gelsolin amyloid neuropathy is slow and quite benign.

In this Review, we describe the clinical manifestations and recent progress in the genetics and treatment of FAP, with special emphasis on TTR amyloidosis, which is by far the most common and devastating disease in this group.

TTR amyloidosis

Andrade first described FAP in north Portugal in 1952.[1] The disease was subsequently reported in Japan (1968)[2] and Sweden (1976).[3] TTR was identified as the precursor of amyloid in this setting, and was found to be synthesised mainly by the liver.[4] The most common pathogenic substitution, Val30Met, was then described and the *TTR* gene was fully sequenced in 1985.[5] In 1990, liver transplantation was undertaken as a therapeutic approach for the treatment of FAP for the first time.[6]

Two main patterns of sensory-motor deficit occur in patients with TTR FAP, both of which are associated with variable autonomic disturbance and extra-neurological manifestations. The most common sensory-motor deficit is nerve length-dependent sensory-motor polyneuropathy; the other type starts with focal deficits resulting from local deposits of amyloid. The pattern and pace of the neurological deficit varies between patients. Some patients with an early-onset presentation deteriorate quickly because of autonomic dysfunction and rapid progression of the sensory-motor deficit. Conversely, in many patients with a late-onset FAP, the polyneuropathy progresses slowly, often with cardiac involvement but with less autonomic dysfunction (figure 1). In other populations, cardiac manifestations are the most prominent symptom, and there is little neurological deficit.

Sensory-motor neuropathy

Length-dependent sensory-motor polyneuropathy

In Portugal, the first symptoms of this pattern of polyneuropathy typically occur in adult patients in their mid-30s; symptom onset is later in Sweden and France. Symptoms start with discomfort in the feet, including numbness and spontaneous pains. At this stage, clinical examination can already detect impaired thermal sensibility over the feet, with decreased pin-prick sensation. However, light touch sensation and proprioception are preserved. Muscle strength and tendon reflexes are normal. This neurological defect typically points to involvement of unmyelinated and small myelinated fibres.[7–9]

A few months after symptom onset, sensory loss has extended above the ankle level on both sides, with

	Transthyretin FAP	Apolipoprotein A-1 FAP	Gelsolin FAP
Geographic distribution	Endemic in Portugal, Sweden and Japan; sporadic presentation worldwide Several thousand cases worldwide	Rare cases	Most cases in Finland (400 cases) but occasional cases worldwide
Transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant
Age at onset	Early onset: third to fourth decade Late onset: sixth to eighth decade	Fourth to fifth decade	Third to fourth decade
Main clinical features	Length-dependent small-fibre sensory-motor polyneuropathy with life-threatening autonomic dysfunction Frequent cardiac and eye involvement	Kidneys, liver, and gastrointestinal tract affected, often leading to organ failure	Corneal lattice dystrophy, cranial neuropathy, and cutis laxa
Diagnosis in familial cases	Family history DNA testing: >100 mutations in *TTR* gene	Family history DNA testing: 16 mutations in *APOA1* gene	Family history DNA testing: one mutation accounts for most cases, another one is extremely rare
Diagnosis in sporadic cases	Amyloid deposits in tissues, identified by nerve biopsy or biopsy of salivary glands or abdominal fat Identification of amyloid type by immunolabelling or mass-spectroscopy-based proteomic analysis DNA testing mandatory	Biopsy of affected organs, immunohistochemistry of amyloid deposits or mass-spectroscopy-based proteomic analysis DNA testing mandatory	Typical eye and skin manifestations DNA testing
Genetics	Val30Met almost the only mutation in Portugal and Sweden: accounts for 50% of mutations worldwide	16 mutations in *APOA1* gene Neuropathic pattern of symptoms associated with Gly26Arg mutation	Single-base mutation at nucleotide 654A in the gelsolin gene on chromosome 9 in Finland
Treatment	Liver transplantation or tafamidis meglumine Treatment of symptoms	Organ transplantation	Plastic surgery

Table: **Characteristics of familial amyloid polyneuropathies (FAPs)**

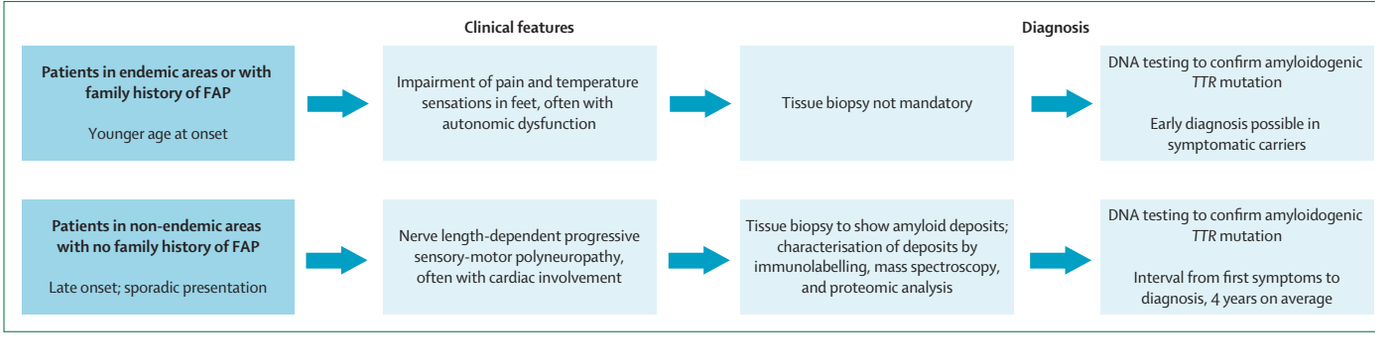

Figure 1: **Clinical presentation and diagnosis of early-onset and late-onset transthyretin familial amyloid polyneuropathy**
The symptomatology and clinical course of transthyretin (TTR) familial amyloid polyneuropathy (FAP) can be highly variable. Typical features of FAP in patients with early-onset and late-onset patterns of TTR amyloidosis are shown, with steps required to confirm the diagnosis.

involvement of light touch distally but with dissociated sensory loss still present proximally. The neurological deficit progresses relentlessly, with extension of sensory loss up the legs. Motor deficit occurs in the feet and lower legs, along with impairment of light touch and deep sensations, in relation to the involvement of larger sensory and motor nerve fibres. Walking becomes increasingly difficult, with loss of balance and stepping gait. Neuropathic pain is often of the burning type, is worse at night, and is associated with allodynia. However, pain is not a symptom in all patients. During the following months and years, the sensory deficit gradually extends to the thighs and then to the upper limbs. The fingers and gradually the forearms are affected as the anterior trunk becomes involved. The motor deficit also follows a length-dependent progression, and walking without an aid becomes increasingly difficult. Life-threatening autonomic dysfunction is present at this stage along with weight loss and muscle wasting. Loss of pain sensation with preservation of normal or subnormal strength can cause patients to experience painless trauma and development of plantar ulcers and foot osteoarthropathy (Charcot joints). However, in some patients, light touch is also affected early, but proprioception is spared in most cases.

Early-onset vs late-onset FAP

Late-onset FAP was identified decades after the early-onset pattern. Differences exist in the presentation of early-onset cases in endemic areas and late-onset cases in non-endemic areas (figure 1). In a series of patients aged over 50 years who had the TTR Val30Met mutation and who were from outside the endemic areas in Japan, there was a 10:1 preponderance of males to females. The most common initial symptom was paraesthesias in the legs, with mild symptoms of autonomic dysfunction, frequent cardiac involvement, low penetrance, and a family history in only one-third of patients.[10,11]

Because of the late onset and low penetrance of TTR mutations in some areas, TTR FAP can present as sporadic cases. We undertook a study of 90 patients (21 women and 69 men) with a mean age of onset of 61 years (range 38–78 years) who presented as non-familial cases in a non-endemic area.[12] Initial manifestations included limb paraesthesias (49 patients) or pain (17 patients), walking difficulty and weakness (five patients), and cardiac or gastrointestinal manifestations (five patients). Mean interval between symptom onset and diagnosis was 4 years (range 1–10 years). At referral, a length-dependent sensory loss affected the legs in two patients, the legs and arms in 20 patients, and legs, arms, and the anterior trunk in 77 patients. Because of the delay between symptom onset and diagnosis, all sensations were affected in 60 patients (67%), whereas small-fibre dysfunction predominated in the other patients.

Focal manifestations at onset

Because of the random distribution of amyloid in the peripheral nervous system, deposits can accumulate locally and induce a focal lesion of a cranial nerve, nerve trunk, or plexus. Carpal tunnel syndrome is a common and early but non-specific manifestation of FAP. Lesions of the median nerve seem more severe when they occur in patients with FAP than when they occur in patients with idiopathic carpal tunnel syndrome,[13] because of the occurrence of endoneurial amyloid deposits associated with nerve entrapment. Besides carpal tunnel syndrome, focal lesions are rare. Only two patients in our series of 90 patients presented with vocal cord paresis at onset, which was in association with pains in the legs.[12]

Autonomic dysfunction

Autonomic neuropathy occurs in most people with early-onset FAP. Cardio-circulatory, gastrointestinal, and genitourinary systems are commonly affected in these patients. Defects in these systems seldom precede the sensory-motor manifestations, with the exception of intracardiac conduction failures. Cardio-circulatory dysautonomia is responsible for orthostatic hypotension, which can remain asymptomatic or can cause fatigue, blurred vision, or dizziness when standing up. Gastrointestinal manifestations include episodic postprandial diarrhoea, severe constipation, or both alternately. Gastroparesis and postprandial vomiting cause dehydration and increase postural hypotension and progressive weight loss. In men, erectile dysfunction is an early feature that might precede sensory symptoms of neuropathy. Urinary symptoms including dysuria and urinary retention occur later. Sweating abnormalities are less frequent. A light-near dissociation (Argyll-Robertson syndrome) of pupillary reactions and irregular and scalloped pupils due to direct involvement of ciliary nerves by local amyloid deposits have been reported.[1] Autonomic dysfunction is less prominent in late-onset FAP. However, in our series of 90 patients with a late-onset sporadic presentation, severe dysautonomia affected 80 patients, including postural hypotension in 52 patients, gastrointestinal dysfunction in 50 patients, impotence in 58 of 69 men, and sphincter disturbance in 31 patients.[12]

CNS involvement

CNS manifestations in TTR amyloidosis are rare despite the occurrence of leptomeningeal amyloid deposition.[14] Dementia, stroke, subarachnoid haemorrhage, ataxia, hydrocephalus, seizures, or fluctuating focal neurological signs have been occasionally reported.[15] Oculoleptomeningeal amyloidosis, in which CNS manifestations and vitreous opacities occur, has been linked to different TTR mutations.[15–18]

Extra-neurological manifestations

Cardiac manifestations

Cardiac involvement is reported in about 80% of cases of TTR FAP, and some cases have an exclusively or predominantly cardiac phenotype. Progressive amyloid deposition can induce restrictive cardiomyopathy, episodes of arrhythmias, and severe conduction disorders, including atrioventricular block with faintness, syncopes, or even sudden death. Atrioventricular block and bundle branch blocks are common and implantation of a pacemaker is often needed. Cardiomyopathy seems to be more common among men with a non-Val30Met mutation and a late onset than in women with a non-Val30Met mutation and late onset.[19,20]

Ocular manifestations

Ocular abnormalities are reported in about 10% of patients with TTR FAP.[21] They include vitreous opacities, which can cause gradual visual loss, and trabecular obstruction, which is responsible for chronic open-angle glaucoma. Scalloped pupils are associated with amyloid deposition in the ciliary nerves.

Renal manifestations

Renal involvement, including a nephritic syndrome and progressive renal failure, occurs in about one-third of patients in Portugal,[22] and in only 6% of patients with sporadic presentation.[12]

Other manifestations

Loss of more than 10% of bodyweight can be an early manifestation of TTR FAP. Cachexia is inescapable after a few years. Patients become bedridden and exposed to bedsores, venous thrombosis, and pulmonary embolism. Cachexia results from gastrointestinal dysautonomia, muscle atrophy by denervation, and infection.

Diagnosis

Clinical examination

At early stages of neuropathy, the presence of disrupted pain and thermal sensations can be difficult to ascertain,

especially in family members of patients. Temperature, light touch, position and vibratory, and pain sensations must be tested, as must muscle strength and tendon reflexes. Motor deficit must be graded and sensory changes recorded on a chart for comparison.

Electrophysiological tests

Results from electromyography and nerve conduction tests are seldom normal, even early in the course of the disease. Sensory action potentials, which are spared in small-fibre neuropathies, are often at the lower limit of normal values initially, but then gradually decrease with progression of the deficit. Quantitative sensory testing and sympathetic skin tests can confirm small-fibre involvement before alteration of sensory action potentials is detected by routine conduction studies.[23–25]

Extra-neurological tests

Cardiac investigations must include echocardiography to detect cardiac enlargement caused by amyloid deposits and electrocardiogram and Holter recording for early detection of intracardiac conduction abnormalities. Cardiac examination, ocular examination, and tests of renal function must be done periodically.

Diagnosis and diagnostic criteria

The diagnosis of FAP rests on the association of a sensory-motor and autonomic polyneuropathy with a family history of neuropathy. In patients with a known family history, TTR FAP should be considered early, when neurological impairment—eg, impaired pain and temperature sensation in the lower limbs—is apparent with or without autonomic manifestations. Presence of amyloid deposits in tissue biopsy is not mandatory in such cases (figure 1).

In patients without a known family history of amyloidosis, TTR FAP should be considered in patients with a progressive axonal polyneuropathy of unknown origin, especially when associated with autonomic dysfunction, cardiac manifestation, or carpal tunnel syndrome. Biopsy of an affected organ, especially a nerve biopsy, can then be done to show the presence of extracellular amyloid deposits in the endoneurial space. Amyloid can also be visualised in muscle specimens, salivary glands, or abdominal fat. However, one must remember that negative biopsy findings do not rule out amyloidosis.

Congo red tinctorial affinity or thioflavin T along with a characteristic yellow-green birefringence under polarised light can be used to confirm the amyloid nature of the sample but not the type of amyloid. Examination by electron microscopy shows the fibrillar aspect of amyloid substance, made up of unbranched fibrils of 10 nm diameter with parallel dense borders. Laser microdissection and mass-spectroscopy-based proteomic analysis can be used to identify the amyloid type.[26] Mass spectroscopy does not specify the site or kind of amino-acid substitution. Immunolabelling with anti-TTR antibody favours the genetic origin of the disease (ie, points to TTR amyloidosis), but DNA testing remains mandatory (figure 1).

Differential diagnosis

When a patient does not have a family history of FAP, a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is often considered first. In CIDP, dysfunction of large myelinated fibres predominates, with slow conduction velocity, high CSF protein content, and virtually no symptoms of dysautonomia. However, in some cases axonal lesions predominate. Additionally, nerve conduction velocity is often decreased in FAP, and CSF protein content can be raised, which might increase the difficulty in differentiating between CIDP and FAP. In such cases, a nerve biopsy can be useful. In our study of 90 patients who presented as non-familial cases, 18 patients had been mistakenly diagnosed and treated for CIDP.[12]

After detection of amyloid in biopsy specimens, the diagnosis of light-chain amyloidosis is often considered because of the high incidence of monoclonal gammopathies in the elderly. Results from amyloid immunolabelling can also be misleading. Mass-spectroscopy-based proteomic analysis can be useful in this setting to differentiate light chain from other types of amyloid deposit. However, *TTR* gene sequencing should be done in all cases (figure 1).[12,27]

Neurobiology and genetics

Pathophysiology of amyloid formation

TTR is a 127-residue polypeptide chain that assembles to form a 56 kDa homotetrameric protein with a prominent β-sheet secondary structure. Its main site of synthesis is the liver, although a small amount is produced by the choroid plexus and retinal cells. TTR circulates in soluble form in the peripheral blood and CSF. Under normal conditions, it transports thyroxin (T4) and retinol.[28] Pathogenic mutations decrease the stability of TTR tetramers and enhance their dissociation into monomers. A complex intracellular process leads to the release of monomers that self-aggregate in the extracellular space, leading to the formation of non-fibrillar soluble oligomers and protofibrils that assemble to create insoluble amyloid fibrils.[29,30]

The *TTR* gene (18q11.2-12) is small (7 kb) and contains four exons. The non-covalent assembly of monomers into tetramers generates the soluble form of TTR.[31] At present, 119 point mutations, including 113 amyloidogenic mutations in the *TTR* gene, have been identified.[32] All are missense point mutations except one microdeletion (ΔVal122). Pathogenic mutations mainly cause neuropathy, but some variants are associated with a predominant or isolated cardiomyopathy termed familial amyloid cardiomyopathy.[33]

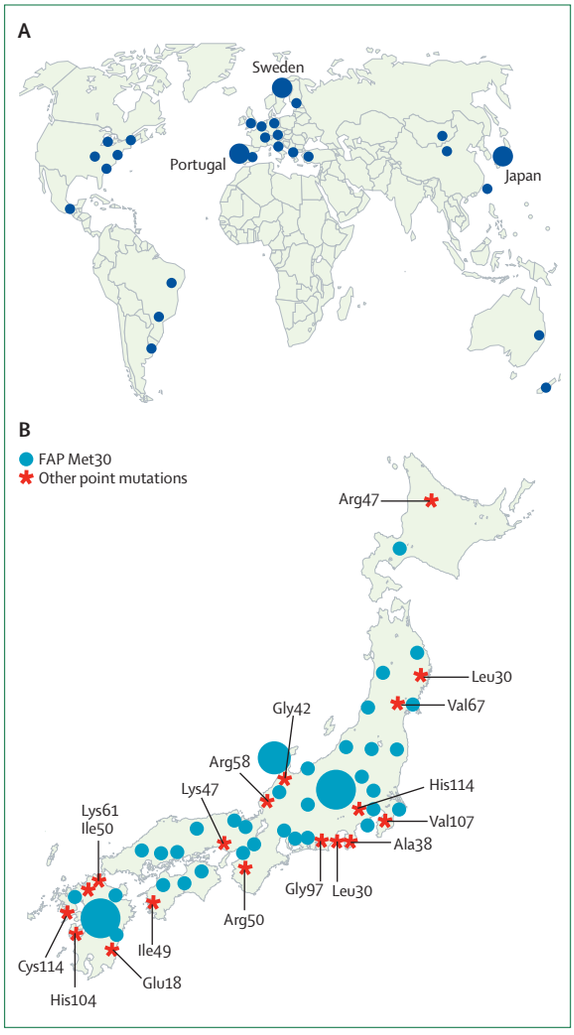

Figure 2: **Geographic distribution of transthyretin familial amyloid polyneuropathy**
(A) World distribution of transthyretin familial amyloid polyneuropathy. (B) Different amyloidogenic mutations reported in Japan outside endemic areas. The size of the circles is proportional to the number of patients. Reproduced from Araki and Ando,[32] by permission of The Japan Academy.

Geographic variations

Figure 2 shows the world distribution of FAP. TTR Val30Met is the most frequent substitution and results from a guanine-to-cytosine mutation in exon 2 of the gene. It is almost the only variant detected in Portugal, Brazil, and Sweden. By contrast, as many as 30 different TTR variants are reported in Japan and France.[32,34,35] A less severe phenotype occurs in patients carrying compound heterozygous mutations, which might enhance the stability of TTR tetramers.[36] Genetic anticipation—that is, earlier onset and a more severe clinical presentation in successive generations—is noted in endemic areas.[37–39]

In the USA, the most common pathogenic variant is Val122Ile, which is detected in up to 3–4% of the African–American population.[33] Its main clinical expression is a hypertrophic restrictive cardiomyopathy with mild or no neurological symptoms.[33] This mutation is also common in west African populations.[33]

Gene penetrance

TTR FAP has been reported throughout the world, particularly in Europe, with strong genotypic heterogeneity.[40] The factors that influence phenotypic variations and the range of ages of onset in families with Val30Met mutations remain unknown. At 80 years of age, penetrance is around 85% in Portugal, Brazil, and France, but only 69% in Sweden.[41,42] However, at intermediate ages, there are large differences in penetrance in different populations. At age 50 years, penetrance is 60% in Portuguese families, but only 18% and 11% in French and Swedish families, respectively.[41,42]

Genetic counselling

Genetic tests can be offered to at-risk family members. DNA testing provides the possibility of presymptomatic predictive diagnosis. These tests are done according to guidelines similar to those used for other autosomal dominant neurodegenerative diseases.[43] Patients taking the tests need psychological support, keeping in mind the late onset in some families and the variable and incomplete penetrance.[41,44] Other predictive methods, such as prenatal diagnosis or preimplantation diagnosis, can be offered on request to affected families with an early age of onset.[45,46]

Pathology and pathophysiology

Amyloid deposits are found in almost every tissue at post-mortem examination. In nerve specimens taken by biopsy or post-mortem examination, amyloid deposits are characteristically found in the endoneurium and around nerve blood vessels (figure 3). At the onset of neuropathic symptoms, the myelinated fibre density remains within normal range, in keeping with clinical and electrophysiological findings (figure 4). Amyloid predominates around endoneurial capillaries, without altering their walls at this stage. As the disease progresses, nerve fibre density is reduced and endoneurial blood vessels are frequently invaded and destroyed by amyloid (figure 4). Destruction of unmyelinated fibres, assessed by electron microscopy, occurs early (figure 5), resulting in loss of pain sensation, which precedes the loss of small and then larger myelinated fibres. Nerve lesions and amyloid deposits are asymmetric between and within fascicles. On teased-fibre preparations, distortion of the nerve fibre and demyelination occur at points of contact with endoneurial clumps of amyloid, which can induce distal axonal degeneration (figure 6). On electron microscopy, Schwann cell basal lamina vanish when in contact with amyloid fibrils, followed by cytoplasmic degenerative changes (figure 7). The susceptibility of Schwann cells to endoneurial amyloid might account for the early loss of unmyelinated fibres, because each Schwann cell harbours several unmyelinated

fibres, versus only one myelinated fibre normally. Loss of Schwann cells can thus impair nutritional support to several unmyelinated fibres and account for their early degeneration. The deleterious effect of endoneurial amyloid deposits occurs through a mechanical effect and probably also through a toxic effect of amyloid fibrils. Destruction of vessel walls by amyloid and occlusion of the lumen are seen only in severely affected nerves (figure 4), making a role for nerve ischaemia unlikely.[14,47] However, amyloid deposits released by the choroid plexus in the subarachnoid space and found around blood vessels penetrating the CNS can occasionally lead to clinical manifestations.[48,49] Eye complications increase with time after liver transplantation in relation to mTTR released by the choroid plexus.[50] The subarachnoid space is in continuity with the endoneurial space, as shown by CSF tracers,[51,52] and there is a proximo-distal fluid convection in the endoneurial space. mTTR can thus follow this route and continue to accumulate in the peripheral nervous system after liver transplantation. However, this process does not account for the peripheral neuropathy noted in recipients of domino transplants.[53,54]

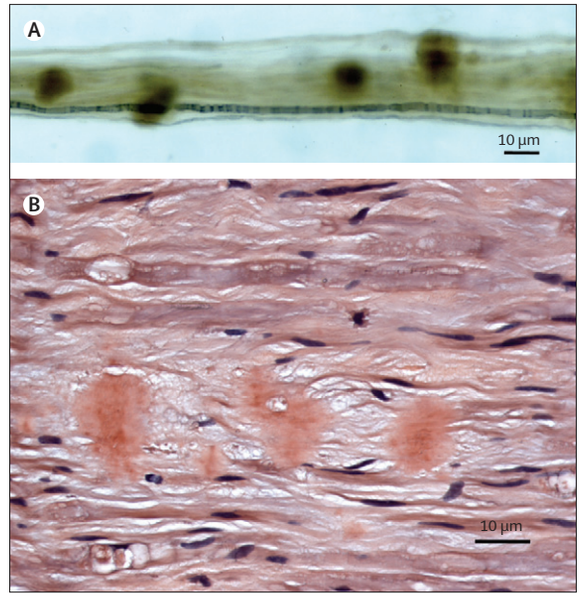

Figure 3: **Amyloid deposits in the endoneurium in transthyretin familial amyloid polyneuropathy**
(A) Teased preparation of the endoneurial content of a nerve biopsy specimen from a 30-year-old man carrying the transthyretin Val30Met mutation. Balls of amyloid deposits can be seen scattered in the endoneurium. Osmium tetroxide stain was used. (B) Longitudinal section of a paraffin-embedded nerve biopsy specimen from a different 30-year-old man carrying the Val30Met mutation. Congo red-stained amyloid deposits can be seen.

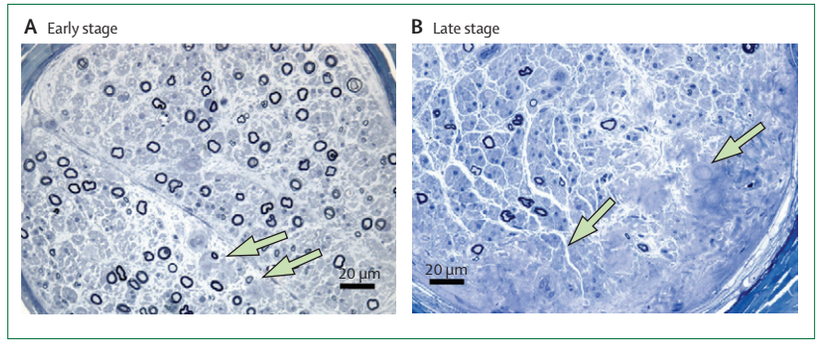

Figure 4: **Pathology at early and late stages of transthyretin familial amyloid polyneuropathy**
(A) 1 µm thick plastic section of a sural nerve biopsy specimen from a 42-year-old woman carrying the Val30Met mutation who had early symptoms of polyneuropathy. Note the presence of small amyloid deposits (arrows) and the preservation of larger myelinated fibres. (B) Sural nerve biopsy specimen from a 39-year-old man with the Val30Met mutation at a late stage of the disease, showing nearly complete disappearance of myelinated fibres and large endoneurial amyloid deposits. At this stage, endoneurial blood vessels are often invaded and destroyed by amyloid (arrows). Thionin blue staining was used on both samples.

Treatment

Treatment of symptoms

Neuropathic pains are common and often quite distressing in FAP. Gabapentin, pregabalin, or duloxetine can be useful in this setting. Tricyclic antidepressants should be used with caution because they can increase orthostatic hypotension. Carpal tunnel syndrome can be alleviated by surgical decompression. Patients with FAP should be given advice about foot care and footwear and about the protection of hyposensitive areas and pressure points, to prevent the occurrence of painless ulcers.

Therapeutic measures for orthostatic hypotension include a salted diet, wearing elastic stockings, and the correction of dehydration induced by vomiting and diarrhoea. Midodrine is given as a first-line pharmacological treatment, but fludrocortisone is often also needed.

Fractioned meals and prokinetic drugs such as domperidone can be used to treat gastroparesis. In the case of profuse vomiting, intravenous rehydration is necessary, coupled with antiemetics such as metoclopramide and vitamin supplementation, as well as with infusions of the prokinetic drug erythromycin. Opioids or subcutaneous injections of octreotide might be needed for the treatment of diarrhoea. Intermittent catheterisation is necessary to improve bladder emptying. Phosphodiesterase inhibitors or intracavernous prostaglandin injections are used to treat erectile dysfunction.

For extra-neurological manifestations, implantation of a permanent pacemaker is needed in many cases. For treatment of arrhythmias, antiarrhythmic drugs might be needed with or without an implantable cardioverter-defibrillator. Dialysis and renal transplantation should be considered at end-stage renal failure. In the case of ocular manifestations, vitrectomy is sometimes needed for vitreous opacities, and trabeculectomy for glaucoma.

Liver transplantation

The aim of liver transplantation is to prevent the formation of additional amyloid deposits by removing the main source of mTTR. Biochemical studies have confirmed the substantial and sustained reduction of serum mTTR after liver transplantation.[6] More than

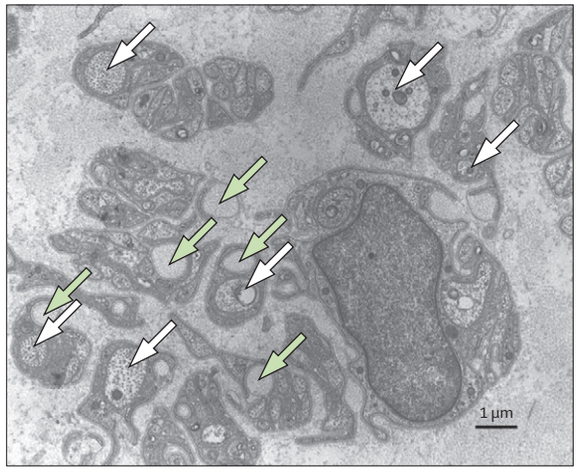

Figure 5: **Destruction of unmyelinated fibres at an early stage of transthyretin amyloidosis**
Electron micrograph of a sural nerve biopsy specimen from a 37-year-old woman carrying the Val30Met mutation at an early stage of transthyretin amyloidosis. Early involvement of unmyelinated fibres can be seen. The white arrows point to normal unmyelinated fibres; the green arrows point to degenerated unmyelinated fibres, which have been replaced by pockets of collagen. The sample was stained by uranyl acetate and lead citrate.

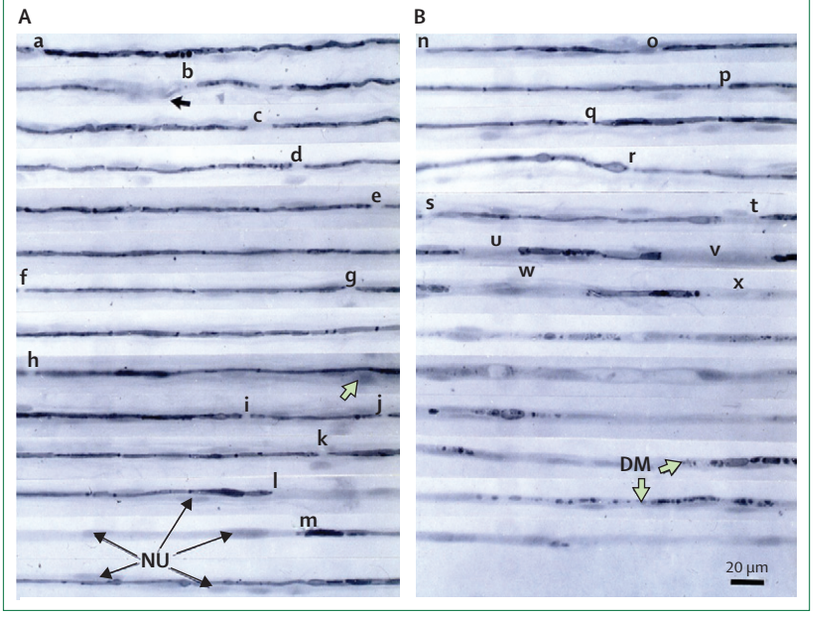

Figure 6: **Axonal degeneration in transthyretin familial amyloid polyneuropathy**
Teased fibre from a sural nerve biopsy of a 34-year-old man with the transthyretin Val30Met mutation. Consecutive segments of an isolated myelinated fibre undergoing axonal degeneration distally are shown. (A) a: proximal end of the isolated segment of the fibre; b and arrow: paranodal demyelination of a node of Ranvier and fibre distortion by an amyloid deposit; c to k: widened nodes of Ranvier; l and m: demyelinated segments. NU=nuclei of Schwann cells. (B) n to w shows gradual widening and demyelination of the nodes of Ranvier. Amyloid deposit distorting the fibre near node o. Distal to node t, larger segments of the fibre are demyelinated, and distal to x, small myelin debris (DM) can be seen towards the end of the isolated fibre, suggesting distal axonal degeneration. Reproduced from Said and colleagues,[9] by permission of Wolters Kluwer Health.

For the **FAP World Transplant Registry** see http://www.fapwtr.org

1500 liver transplantation procedures were done from cadaveric or living donors between 1990 and 2009 according to the FAP World Transplant Registry, mostly (>80%) in patients with the Val30Met mutation.[55] Explanted FAP livers can be used as donor grafts in domino liver transplantation.

Although controlled studies to assess the efficacy of liver transplantation have not been done, the method seems to be beneficial in patients with the Val30Met mutation, whose median survival is now greater than 20 years.[56] In Sweden, the 5-year survival rate is now 92%.[57] However, among patients with the Val30Met mutation who have disease onset after 50 years, survival does not differ between grafted patients and non-grafted historical controls.[55,56] Among these grafted patients, the survival of men is lower than that of women, possibly because of the increased prevalence and severity of heart problems in men aged over 50 years.[19,58,59] Liver transplantation does not prevent the development of heart arrhythmia, which requires pacemaker insertion. The development of arrhythmia is unrelated to sex or age at disease onset and the yearly risk does not seem to decrease with time after liver transplantation.[60]

By contrast, the 5-year survival rate of patients who do not have the Val30Met mutation is significantly lower than that of patients with TTR Val30Met.[55] Independent negative prognostic factors include non-Val30Met genotypes, malnutrition (low body mass index), autonomic dysfunction, and patients with severe polyneuropathy who need an aid for walking. The prognostic value of a late age at onset remains unclear.

Liver transplantation must be done early in the course of FAP. Over 90% of patients with pure sensory neuropathy remain stable after liver transplantation,[57] although no significant objective improvement of amyloid neuropathy occurs. The main factor affecting prognosis after liver transplantation is the occurrence or worsening of cardiac dysfunction.[57,58] Liver transplantation has no effect on ocular complications or eventual CNS symptoms of amyloidosis caused by the persistent synthesis of mTTR by retinal epithelial cells and the choroid plexus.[61] In a recent survey of outcome after liver transplantation, progression of ocular amyloidosis was noted in 17 (50%) of 34 patients, 13 of whom had de-novo amyloid deposits in the vitreous body; progression of cardiac amyloidosis was reported in ten patients (29%).[62]

Transmission of TTR amyloidosis by means of domino liver transplantation has been documented in recipients of FAP livers.[53,54] Symptomatic neuropathy seems to occur after a minimum of 5 years after liver transplantation and might warrant retransplantation. Risk factors for this complication are being assessed.

Liver transplantation should be an early consideration in any patient who presents with symptomatic TTR FAP. In the presence of severe concomitant organ failure, a combined organ transplant should be considered (ie, liver and heart or liver and kidney transplantation). By contrast, liver transplantation is not an option for asymptomatic mutation carriers because of the incomplete penetrance of pathogenic mutations. Contraindications to liver transplantation include the presence

of a severe polyneuropathy or severe autonomic dysfunction and a poor nutritional status. Severe cardiac amyloidosis precludes liver transplantation if a combined heart and liver transplantation is not feasible, because heart involvement might progress despite liver transplantation.

Heart and nerve involvement might progress after liver transplantation. Amyloid deposits in the heart usually contain 50–70% mTTR, compared with up to 75–90% of amyloid composed of wild-type TTR in post-mortem cardiac tissue and nerves in transplanted individuals.[63–65] On the basis of these data, progression of cardiac amyloidosis is hypothesised to result from the continued deposition of wild-type TTR on pre-existing amyloid deposits. By contrast, in peripheral nerves the composition of deposits either remains identical to that of non-grafted patients or reverses, suggesting the accumulation of wild-type TTR in the latter situation.[65] The former situation suggests that the progression of neuropathy after liver transplantation might also result from the continued deposition of mTTR secreted by the choroid plexus, which directly communicates with the endoneurial space through the subarachnoid space.[36,66]

Medical treatment

TTR stabilisers are pharmacological chaperones of TTR that bind specifically to the tetramers and increase their stability, thereby preventing tetramer dissociation into monomers, which is the rate-limiting step in amyloid fibril formation.[67,68] Two drugs, diflunisal (NCT00294671) and tafamidis meglumine (NCT01435655), are undergoing clinical development. In a pivotal phase 2/3 randomised, double-blind, placebo-controlled trial, neuropathy did not progress in 60% of patients who received tafamidis meglumine versus 38% of the placebo group.[69] Neurological deterioration was decreased by 52%; quality of life and modified BMI were maintained under tafamidis meglumine and worsened under placebo.

Gene therapy is a promising future therapeutic strategy for TTR amyloidosis, although many considerations need to be addressed. In recent years, this therapy has mainly focused on strategies to suppress variant TTR gene expression through degradation of TTR messenger RNA. This strategy has been attempted with small interfering RNAs,[70] antisense oligonucleotides,[71] or specific cleavage by ribozymes.[72,73] At present, these strategies are not available for patients, and there are no clinical data.

Prognosis

Current approaches to the management of patients with TTR FAP—including prevention of fatal cardiac events by implantation of pacemakers, treatment of postural hypotension, prevention and treatment of infection, and improved nutrition—have substantially improved their survival and quality of life. The effect of liver transplantation seems to be marked when done early in the course of the disease, but does not prevent the deterioration of cardiac symptoms. Recipients of liver transplants have to remain on immunosuppressive treatment, which exposes them to other complications (eg, infections). Quality of life is improved in patients treated with tafamidis, which is well tolerated,[69] but its long-term efficacy in the treatment of neuropathy remains to be seen.

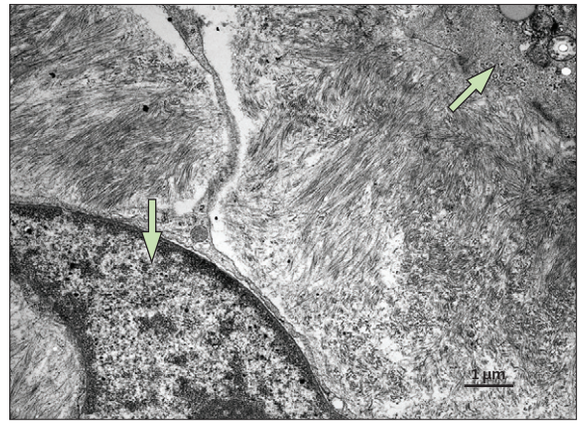

Figure 7: **Schwann cell degeneration in contact with endoneurial amyloid deposit in transthyretin familial amyloid polyneuropathy**
Electron micrograph of a sural nerve biopsy specimen from a 34-year-old man carrying the transthyretin Val30Met mutation. The fibrillary structure of amyloid and the destruction of endoneurial cells can be seen. At the right upper corner of the photograph a Schwann cell is degenerating, while at the left lower corner a fibroblast can still be identified. Sample was stained with uranyl acetate and lead citrate.

Apolipoprotein A-1 amyloidosis

Clinical aspects and diagnosis

Originally described in Iowa by van Allen and colleagues in 1969,[74] apolipoprotein A-1 amyloidosis is characterised by polysystemic manifestations with onset in the fourth decade of life. The disease predominantly affects the kidney, liver, and gastrointestinal tract. A length-dependent polyneuropathy occurs but is not a prominent feature of the disease. Progression of renal lesions can lead to chronic renal failure, dialysis, and related polyneuropathy. Amyloid deposits, which strongly react with an anti-apolipoprotein A-1 antibody, can be found in most organs.

Neurobiology and genetics

Apolipoprotein A-1 is a 28 kDa plasma protein synthesised by the liver and the small intestine. Mature apolipoprotein A-1 consists of 243 aminoacids encoded by exons 3 and 4 of the *APOA1* gene.[75] 16 mutations of the *APOA1* gene are associated with hereditary apolipoprotein A-1 amyloidosis.[76] Most of the germline mutations are nucleotide substitutions, but two variants are caused by deletions and another one is caused by a deletion/insertion mutation. Patients with gene

mutations affecting residues 1–75 mainly suffer from hepatic and renal amyloidosis, whereas mutations in codons 173–178 cause amyloidosis of the heart, larynx, and skin. The neuropathic pattern of symptoms is associated with the Gly26Arg mutation, which has also been found in non-neuropathic forms of apolipoprotein A-1 amyloidosis.[77,78]

Treatment

There is no specific treatment for apolipoprotein A-1 FAP. Hepatorenal transplantation has been done in a patient with the Gly26Arg mutation who had end-stage renal failure and progressive peripheral neuropathy.[79] Plasma concentration of the apolipoprotein A-1 variant decreased by over 50% after transplantation, with progressive improvement of the neuropathic symptoms, which probably resulted from improved renal function. In patients with neuropathy, treatment of symptoms is the same as for those with TTR FAP.

Gelsolin amyloidosis

Hereditary gelsolin amyloidosis (HGA) is an autosomal dominant systemic amyloidosis, first described in 1969 in Finland.[80] HGA is characterised by adult onset of slowly progressive neurological deterioration, with corneal lattice dystrophy, cranial neuropathy, and cutis laxa. A mutation in the gelsolin gene leads to the generation of amyloid fibrils that are composed of fragments of gelsolin.[81,82] Most patients with HGA have been reported in Finland.[83,84] The estimated number of Finnish patients with HGA was 400 in 1998.[85] Occasional symptomatic cases have been reported worldwide.

Clinical aspects

HGA is characterised by a triad of neurological, ophthalmological, and dermatological manifestations, variably associated with systemic manifestations, including cardiac, renal, and pharyngeal abnormalities.[85] The first manifestations occur at age 25–30 years with corneal lattice dystrophy followed by slowly progressive cranial neuropathy and cutis laxa, leading to severe disability at an advanced age. Life-threatening renal or cardiac complications are rare.[84,86]

Cranial nerve involvement is the predominant neurological manifestation in HGA. The upper branch of the facial nerve is affected first. Hypoglossal nerve involvement is frequent, sometimes combined with glossopharyngeal and vagal neuropathy, and can substantially impair daily living at advanced age. A predominantly sensory peripheral neuropathy is detected after 40–50 years of age. The feet are usually affected first, which rarely leads to sensory ataxia in elderly patients.[87] Minor autonomic neuropathy occurs.[88,89] HGA can manifest with cardiac conduction defects, which can result in patients needing a pacemaker. Corneal lattice dystrophy is often the first disease manifestation detected before age 30 years.[84,90] Abnormal skin laxity, cutis laxa,[91] or early skin ageing is a major manifestation of the disease, causing serious handicap that needs plastic surgery.[92]

Amyloid angiopathy can involve spinal and cerebral blood vessels.[93] In homozygous forms, the disease has an earlier onset with a fatal outcome, sometimes before 30 years of age.[84,94]

Diagnosis

The clinical diagnosis of HGA rests on association of corneal lattice dystrophy with typical bilateral facial pareses and laxity of the skin. In cases where the facial expressions typical of this disorder develop quickly, cutaneous T-cell lymphoma should be excluded. Biopsies are usually not needed because the diagnosis can be confirmed by DNA testing.

Neurobiology and genetics

Gelsolin is a calcium-dependent, multifunctional regulator of actin filament dynamics. A single mutation within the type 2 metal ion-binding site is the cause of the Finnish type, which is characterised by the extracellular deposition of a 71-residue fragment of gelsolin.[95] In Finland, all patients carry the single base mutation at nucleotide 654A in the gelsolin gene on chromosome 9.[81,94] In some populations outside Finland, HGA is caused by a G654T gelsolin mutation.[96]

Pathology

The gelsolin-derived nature of the amyloid deposits can be shown by use of rabbit antisera. Amyloid deposits are found in the eyes, skin, and peripheral nerves, especially in the perineurium and epineurium. Amyloid angiopathy affects the arteries of nearly every organ.

Treatment

Good ophthalmological care is particularly important. Surgical intervention is often needed to correct facial laxity.[92] There is so far no treatment to prevent gelsolin-derived amyloid formation.

Conclusion

FAP represents a heterogeneous group of autosomal dominant hereditary disorders characterised by tissue deposition of amyloid fibrils. The most common and by far the most severe form of FAP is caused by mutations in the *TTR* gene, which is responsible for the FAP that was originally reported in Portugal and that is found worldwide. Many mutations in the *TTR* gene have been identified, and progress has been made in diagnostic procedures and genetic counselling. Because TTR is secreted mainly by the liver, early liver transplantation is now recommended for patients with symptomatic neuropathy caused by the Val30Met mutation. Additionally, tafamidis meglumine, a recently introduced TTR stabiliser, seems to favourably influence the course of the disease. Gene therapy can be expected for

Search strategy

References for this Review were identified through searches of PubMed from 1950 to September, 2011, with the search terms "amyloidosis", "familial amyloidosis", "liver transplantation", "apolipoprotein A-1", and "gelsolin". References were also identified from our own files. Only papers in English were reviewed. The final reference list was based on original publications and practical interest.

this disorder in the not-too-distant future. There is a need for diagnostic criteria for the early detection of symptomatic neuropathy in carriers of an amyloidogenic mutation, which would allow more efficacious therapeutic intervention. Apolipoprotein A-1 FAP is extremely rare and causes life-threatening multisystem manifestations with occasional neuropathy. So far, only early detection of organ involvement by amyloid deposition and organ transplantation can improve the outcome of apolipoprotein A-1 FAP. Gelsolin FAP is almost only observed in Finland, with only occasional cases elsewhere. The neuropathy is not the major burden in this disorder, which is dominated by skin changes and cranial nerve involvement. This disease does not markedly shorten the life expectancy of affected individuals but greatly impairs quality of life. Interest is targeted towards inhibition and elimination of abnormal gelsolin by specific enzyme inhibitors. Despite advances in our understanding of FAP, the prognosis for many patients affected by this group of disorders remains bleak. Within the next decade, we hope to see improvements in the early diagnosis and treatment of these often devastating diseases.

Contributors

VP-B and GS contributed equally to the writing and revision of the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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