J Neurol (2001) 248 : 647–657

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Hereditary and acquired amyloid neuropathies

Abstract Amyloid neuropathies occur in a context of hereditary (FAP) or acquired amyloidosis. They present usually as severe and progressive polyneuropathy and carry a poor prognosis. Most FAP are associated with endoneurial deposits of variant transthyretin (TTR) with substitution of one aminoacid and are secondary to a point mutation of the TTR gene. Portugal is the main endemic area of TTR-FAP, secondary to point mutation of exon 2. However, around the world, 50 other TTR gene mutations have been recently reported, each one in few families. Genetic studies are useful for diagnosis of FAP in patients with a positive family history and for identification of the cause of seemingly sporadic cases. TTR gene analysis is also useful for genetic counselling including antenatal diagnosis in variants with early onset. Gelsolin-FAP are the second variety and present as a benign cranial and sensory polyneuropathy and affect essentially Finnish patients. Acquired amyloid neuropathy concerns only immunoglobulin light chain amyloidosis (AL) and are frequently associated with renal manifestations and monoclonal protein in serum or urine. Specific treatment of amyloid polyneuropathy varies with the variety of amyloidosis including liver transplantation in TTR-FAP, at the onset of the disease or chemotherapy for immunoglobulin light chain amyloidosis.

Key words Familial amyloid polyneuropathy · Transthyretin · Immunoglobulins · Light-Chain · Amyloid · Polyneuropathies

Received: 8 March 2001
Accepted: 12 March 2001

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Introduction

Amyloid neuropathies encompass the neurological manifestations related to lesions of the peripheral nervous system associated with amyloid deposits in the endoneurium. Isolated carpal tunnel syndrome secondary to amyloid deposit in the flexor reticulum as seen in patients undergoing hemodialysis with amyloid deposits made of β2 microglobulin is thus excluded. Since the first description of amyloid neuropathy in 1924, many cases have been reported, subdivided into hereditary (FAP) and acquired forms. In this review, we will describe recent advances concerning diagnosis and management of amyloid neuropathies. During the last fifteen years, a biochemical heterogeneity of amyloidogenic proteins has been established in FAP [23, 37, 51], opening the way to specific therapies. Identification of genetic mutations responsible for the synthesis of these proteins has allowed familial detection and genetic counselling by molecular biology [52, 53].

Classification (Table 1)

Amyloid neuropathies may be encountered in hereditary forms or in systemic acquired amyloidosis.

Familial amyloid polyneuropathies (FAP)

The Portuguese variant initially described by Andrade [6] in Povoa de Varzim in North of Portugal, is by far the most common through the world. A positive family

Tab. 1 Classification of Amyloid Neuropathy according to amyloidogenic protein.

	Familial amyloidotic polyneuropathy [FAP]		Acquired amyloid neuropathy
Amyloidogenic Protein	Variant TTR Val30Met (+++) Other variants: n=50	Gelsolin Asp187asn	Fragment of immunoglobulin light chain (AL)
Clinical aspects			
Neuropathy	Distal symmetrical sensorymotor polyneuropathy Autonomic dysfunction	Cranial (+++) Sensory polyneuropathy	Sensorymotor polyneuropathy Autonomic dysfunction
Other manifestations	Weight loss Heart dysfunction (+++) Ocular (+) (Vitreous opacity, intraocular pressure) Leptomeningeal	Corneal Dystrophy	Nephrotic syndrome Renal failure Heart failure Weight loss
Biological Investigations	*Genetic test* Gene mutation		*Serum & urine Immunoelectrophoresis* Monoclonal protein
	TTR	Gelsolin	
Geographic areas	Ubiquitous Portugal (500 families)* Sweden*, Japan, France Other countries	Finland (400 cases) Japan, USA (20 cases)	Ubiquitous (Rare)
Positive family story	0 (sporadic cases) 95 % (Portugal)	100 %	0
Mean Survival after onset (years)	10	Not modified	3

TTR : transthyretin. *: associated only with Val30Met TTR variant. In this table, apolipoprotein FAP variant has been omitted as it concerns only one family in USA.

story is usually found in FAP patients because their inheritance is autosomal dominant and the penetrance high. The initial classification proposed for familial amyloid polyneuropathy took presentation of the neuropathy and associated non-neurological manifestations into account [22]. Modern classification of FAP is based on the nature of the precursor plasma proteins that form the fibril deposits, helped by genetic studies: variant transthyretin (TTR), fragments of gelsolin or apolipoprotein A1 (Table 1). TTR-FAP are by far the most common variants through the world.

Neuropathies in systemic acquired amyloidoses

Neuropathy may occur in systemic acquired amyloidosis [20] but only in immunoglobulin light chain amyloidosis (AL) [2, 31, 32], for which amyloid fibrils are fragments of immunoglobulin light chain. Monoclonal immunoglobulins or light chains are detected in serum and/or urine in 75 % of these patients at referral [2, 20]. In 40 % of patients, amyloid neuropathy occurs in a context of overt malignant lymphoproliferative disorders [2] including multiple myeloma [2, 14, 31, 55] or Waldenström macroglobulinemia [2, 9, 10, 39] which are usually diagnosed at the time of the neuropathy. Neuropathy does not occur in secondary "AA" amyloidosis which may complicate chronic inflammatory or infectious diseases [20].

Seemingly sporadic cases of amyloid neuropathy

Until recently, a subgroup of patients with amyloid neuropathies defied classification owing to the absence of a family history to suggest FAP and serum monoclonal immunoglobulin components which might link them to "AL" amyloidosis. Genetic studies in these patients have shown a TTR gene point mutation in most of them [36, 43] allowing their inclusion in the largest group of hereditary neuropathies.

Clinical Aspects

Age at onset and sex ratio

Amyloid neuropathies occur in adults with a variable age at onset of the first symptoms. It can be in the third decade as in endemic areas of FAP in Portugal [16] or Japan but later in the sixth or seventh decade in Sweden or apparently sporadic cases [36, 43] and in immunoglobulin light chain amyloidosis [2, 31]. The incidence of neuropathy is usually equal for both sexes, but male predominance is observed in seemingly sporadic cases of FAP [36].

Clinical presentation of the neuropathy (Table 2)

Distal symmetrical sensory or sensorymotor polyneuropathy with or without autonomic disturbances

Amyloid neuropathy usually presents as a progressive sensory or sensorimotor polyneuropathy with or without autonomic disturbances [16, 31]. Sensory symptoms are usually the first evidence of neuropathy. Manifestations include : distal paresthesiae, numbness, sometimes in association with burning or pseudoradicular pains. In some cases, trophic lesions secondary to thermal and pain anesthesia may also be a presenting feature of the neuropathy. They lead to perforating foot ulcers or painless burning in the extremities. On examination, superficial sensory loss is usually dissociated and more pronounced for pain and temperature than for light touch. Position and vibration sense are usually spared in the first years. The distribution and progression of superficial sensory loss is characteristic of a length dependent axonal polyneuropathy [48]. In due course, symmetrical and distal sensory loss extends to the proximal part of the lower limbs and appears later in the hands. In the advanced stage, all four extremities, anterior and median parts of the trunk, and the scalp as a "calotte" are affected. Errors in joint position sense and vibration sensation loss in lower limbs with astereognosia appear at this stage. In neuropathies of systemic amyloidosis of "AL" type, superficial sensory loss is not dissociated in half of the cases [31].

Weakness appears after sensory loss predominantly in the distal part of the lower limbs, and may sometimes be asymmetrical, suggesting neuritis multiplex. Slight weakness of the extensors of the big toes is seen at the beginning, followed later by weakness of extensors and flexors of the feet with foot drop. Weakness may progress to a distal paralysis of all four extremities [16, 31]. Neuroarthropathies (Charcot's joints) may occur.

Autonomic disturbances are frequent and may be the first sign of the disease. When present with polyneuropathy and in the absence of diabetes mellitus, the diagnosis of amyloidosis is likely. Gastrointestinal symptoms are often seen. They are usually marked by typical alternating diarrhea and constipation but also obstinate constipation, or daily diarrhea. The diarrhea is triggered by meals or may be nocturnal and often explosive. Gastroparesis may be manifest as anorexia, early satiety, a persistent sense of gastric fullness. More rarely, recurrent vomiting may occur usually for periods of 1 or 4 days and may lead to weight loss and malnutrition. Postural hypotension may be responsible of dizziness, fainting or may be asymptomatic. Sometimes, orthostatic hypotension may dominate the clinical picture and force the patient to be beddriden [13]. Among the genitourinary disorders, impotence occurs early; urinary disorders are seen later and may include dysuria, urinary retention or urinary incontinence. Urinary infections may reveal urinary bladder dysfunction. Trunkal hyperhydrosis crisis may also occur often triggered by meals. On examination, pupillary disturbances with weakening of pupillary reaction to light, irregular and scalloped edges or Argyll Robertson sign may be found.

Rare features

Occasionally, polyneuropathy may be absent and may be limited to cranial nerves or to focal neuropathy.

Cranial neuropathy: In the familial amyloidosis of the Finnish type, there is a progressive involvement of cranial nerves with sparing of oculomotor nerves. The upper branch of facial nerve is initially affected in the fourth decade [33, 35] and other cranial nerves are later involved including trigeminal nerve, VIII with impaired hearing and hypoglossal nerve. Moderate sensory polyneuropathy is usually associated. The estimated total number of living patients in Finland is about 400 ; about twenty cases have been reported outside Finland

Tab. 2 Clinical features suggestive of amyloid neuropathy.

Clinical manifestations	*Context*
1. Progressive distal symmetrical sensory polyneuropathy Predominantly pain and thermal sensory loss (+++)	A. Absence of diabetes B. Positive family story of FAP C. Monoclonal gammopathy (benign or malignant)
2. Progressive distal symmetrical sensorymotor polyneuropathy	*Electrophysiological study* D. Axonal pattern
3. Autonomic dysfunction	
4. Other manifestations: Neuritis multiplex Carpal tunnel syndrome, Cranial neuropathy, ...	

Situations suggestive of amyloid neuropathy	
■ (1+3) & A	■ (1 + 3) & (C + D)
■ (1 or 2 or 3) & B	■ (2 + 3) & (C + D)
■ (1 or 2) & D & unknown origin	■ 4

including Japan and United States. Cranial neuropathy has been occasionally reported in AL amyloidosis [64].

Carpal tunnel syndrome: Carpal tunnel syndrome may be the earliest manifestation in some FAP and precedes a sensory motor polyneuropathy by several years [28, 47]. It may also occur in neuropathies of AL amyloidosis [10, 31]. It is important to recognize this syndrome because division of the flexor retinaculum may result in complete resolution of symptoms [47].

Rarely, a focal involvement of the sacral plexus [7] or lumbosacral roots have been reported.

Non neurological manifestations

Non neurological manifestations may occur in patients with amyloid neuropathies. They are secondary to systemic distribution of amyloid deposits as seen in postmortem studies [6, 61] and vary according to the amyloidogenic protein (*Table 1*).

Cardiac manifestations: Cardiac manifestations are frequent. They may include conduction or rhythm disturbances [17] as usually seen in FAP in Portugal or Sweden. The prevalence and severity of heart conduction disturbances which worsen with time [41] justify regular medical evaluation with electrocardiograms. Manifestations of cardiac insufficiency concomitant with diffuse myocardial amyloid infiltration are reported in AL amyloidosis [20, 31] but also in a few TTR-FAP [54, 58].

Other manifestations

Renal involvement is frequent and severe in immunoglobulin light chain amyloidosis marked by nephrotic syndrome or renal insufficiency and is present at the time of diagnosis of neuropathy in 25 % of patients [2, 31]. In FAP, renal involvement is mild and occurs late in the course. Ocular manifestations are frequent in TTR FAP, including vitreous opacities and intraocular pressure leading in some cases to blindness. In the Finnish variant of FAP, corneal lattice dystrophy and skin changes accompany the cranial and peripheral neuropathy [33, 35]. A severe loss of weight usually accompanies immunoglobulin light chain and TTR amyloid polyneuropathy.

Course

Amyloid neuropathy is slowly progressive leading to increasing disability. The prototypical course of neuropathy in FAP has allowed definition of three stages in Portuguese patients [16]. In stage I, there is a predominantly sensory neuropathy in the lower limbs. The patient is still walking without any help. Stage II occurs after a mean interval of 5.6 years marked by a sensorimotor polyneuropathy; motor signs progress in the lower limbs with steppage gait, affecting later distally upper limbs. Later, difficulties in walking progress requiring ambulation aids. In stage III, the patient is beddriden or confined to a wheelchair after a mean interval of 10.4 years. Temperature and pain are not felt all over the body except for the head and neck. The course of immunoglobulin light chain amyloid neuropathies is identical [31], but seems more frequently associated with refractory pains requiring opiates [2]. At advances stages, most patients have disabling autonomic dysfunction including severe diarrhea, urinary incontinence and postural hypotension.

Survival

The length of survival for patients with amyloid neuropathy is usually severely shortened. TTR-FAP patients usually die after a mean interval of 10 years from the first symptoms, after progressive worsening of the neuropathy, from secondary infections, cachexia or suddenly [16]. The course may be shorter in variants associated with severe cardiomyopathy [54, 58]. Survival of patients with immunoglobulin light chain amyloid neuropathy is considerably shorter than in FAP with a median survival of only 2 years after diagnosis [2, 31]. These patients die from congestive heart failure or suddenly. Conversely, the course is benign for patients with gelsolin-FAP with survival to the same as that of unaffected family members [35].

Electrophysiological aspects

Electrophysiological study shows signs in favor of an axonal polyneuropathy affecting early sensory fibers [31, 50]. Sensory nerve action potential (SNAP)'s amplitudes are diminished with preservation of nerve conduction velocities and usually are not recordable in lower limbs at the time of diagnosis [31, 50]. They may be preserved in patients presenting with predominantly autonomic dysfunction and mild sensory neuropathy because of predominantly small fiber involvement. Autonomic neuropathy may be studied with non invasive cardiovascular tests such as variation of heart rate (R-R space) in deep breething, Valsalva maneuver and orthostatism. A lesser variation of cardiac frequency is seen in affected patients as compared with more pronounced disturbances as the disease progresses [40].

Histopathology

Nerve biopsy usually allows the diagnosis of amyloid neuropathy to be established by identifying amyloid deposits in the endoneurium and always shows a progressive axonal neuropathy. Lack of visualization of amyloid deposits does not exclude the diagnosis. Nerve biopsy has been replaced recently by genetic studies in patients with a positive family history of FAP. Amyloid deposits have some characteristics on light microscopy: red Congo staining and green birefringence in the polarizing microscope. Size and number of deposits are variable. They can be large and numerous, nodular or diffuse, predominating around vessels in the endoneurium or in the subperineurial space, or sometimes tiny. Sensitivity of nerve biopsy to identify amyloid deposits increases when serial sections of nerve embedded in paraffin are examined. By electron microscopic examination, amyloid deposits are characterized by unbranched fibrils of indeterminate length and of 7.5 to 10 nm diameter in cross section [57]. In the absence of deposits on nerve biopsy, diagnosis of amyloid neuropathy may require biopsy of other tissue including accessory salivary glands, rectal submucosa, skin or kidney. Nerve biopsy always shows progressive axonal lesions with fibers undergoing Wallerian degeneration and myelinated fiber loss predominating on small myelinated fibers, visible on semi-thin sections [18, 48, 63] and early loss of nonmyelinated fibers when studied by electron microscopy. Immunohistochemical studies are theorically useful to determine the biochemical nature of amyloid deposits: transthyretin, light chains, gelsolin, apolipoprotein A1, but in our experience, their specificity is incomplete. Single fiber analysis which allows study of morphology of dissociated myelinated fibers on the nerve biopsied shows fibers undergoing Wallerian degeneration and segmental abnormalities of the myelin sheath with segmental demyelination and remyelination sometimes close to amyloid deposits [18, 48], distal axonal degeneration and regeneration by sprouting of intact axonal end [48].

Pathophysiology

Several hypothesis have been suggested to explain pathogenesis of the neuropathy in amyloidosis. The first one supposed an ischemic mechanism because of the finding of amyloid deposits in the walls of vasa nervorum. That hypothesis seems to be unlikely to be correct because non myelinated fibers and small myelinated fibers, which are more severely and early affected in amyloid neuropathies are less sensitive to ischemia [21]. The second hypothesis concerns a mechanical process secondary to nerve fiber compression by amyloid deposits [18, 48]. Multifocal staged lesions of nerve fibers in dorsal root ganglia, plexuses and distal trunks [24] could explain distal axonal degeneration of fibres. We cannot exclude a toxic or metabolic effect of amyloid deposits on endoneurial structures [48]. The predominance of non myelinated fiber injury is unexplained, but myelin sheath could have a protective role against modifications of endoneurial space content.

Biochemical aspects

Amyloidogenic proteins are various in amyloid neuropathy. The most common constituent fibril protein in FAP is by far a variant abnormal transthyretin (TTR) with single amino acid substitution [51]. TTR is a tetramer (55 KDa) composed of four identical monomer subunits. Each monomer shows an extensive β pleated structure. The mature protein has two major functions: binding of plasma thyroxine, and to retinol binding proteins. Its amyloidogenic potential is presumed to be partly due to its extensive β pleated structure. TTR is synthetized by liver, choroid plexus and retinal epithelium. In Finnish FAP, amyloid fibrils are composed of the internal degradation products of an abnormal fragment of gelsolin beginning at position 173 of plasma gelsolin [23] with actin modulating properties. Finally, apolipoprotein A-I has been found to the constituent protein in only one family in Iowa [37]. For neuropathies of systemic acquired amyloidosis (AL), the subunit protein is the variable portion of immunoglobulin light chains.

Genetics aspects

FAP are autosomal dominant transmission diseases. During the last decade, important progress have allowed identification of genetic abnormalities responsible for the synthesis of different amyloidogenic proteins in FAP which may be detected by different molecular biology techniques. That has considerably modified the management of patients with amyloid polyneuropathy.

FAP related to a variant transthyretin

Most of FAP are related to TTR gene mutation. TTR gene is located on chromosome 18 and is 7 kb long, with four exons of ~ 200 base pairs each and three introns. Exon 1 contains the coding sequences for only the first three aminoacids of the mature protein, whereas the other exons code for the remainder of the polypeptide chain, i. e. residues 4–47 (exon 2), residues 48–92 (exon 3) and residues 93–127 (exon 4) [52].

FAP secondary to Val → Met30 TTR variant

Structural modification of TTR (val → met 30) which results from a point mutation in the second exon of the TTR gene is the most frequent one around the world. This genetic abnormality is present in major endemic areas : Portuguese, Swedish and in most Japanese families. More recently, it has been shown in half of the French families [43]. The haplotype studies using TTR intron polymorphisms suggest more than one founder for this mutation, as recently shown in French patients, with different disease-associated haplotype in patients of Portuguese descent from those of French descent [46]. More than 50 other mutations for TTR gene have been described in families with amyloid neuropathy [52], usually characterized in only one family (Table 3). Recently, a family with FAP has been reported associated with DNA deletion in the TTR gene [65].

FAP secondary to other TTR variants

For the non-met30 TTR variants, clinical presentation of the neuropathy is usually similar to the Portuguese neuropathy but sometimes is preceded by a carpal tunnel syndrome from many years [28] or associated with a severe cardiomyopathy [54, 58], or symptoms of leptomeningeal amyloid including seizures and recurrent subarachnoid hemorrhage [12].

Genetic study in seemingly sporadic cases of amyloid neuropathy

Genetic studies are very useful in the management of apparently sporadic cases of amyloid neuropathy as they can demonstrate their hereditary origin and label them as hereditary forms: in endemic areas [36] or in lesser risk areas [43]. As an exemple, in France more than 50 FAP cases of French origin have been diagnosed during the last decade with the help of genetic studies [43]. They fulfill many characteristics including sporadic presentation in 2/3 of cases, late onset (mean age 53 years) and genetic heterogeneity with 12 TTR gene mutations versus only one in Portugal.

Genetic counselling

Genetic counselling is an important mean of control in FAP with early onset, as in Portugal, because transmission is autosomal dominant, and prognosis of the affection is grave. Prenatal diagnosis is possible after trophoblast biopsy after the 10^{th} week of amenorrhea [3] in mothers carrying genetic abnormality and therapeutic interruption of pregnancy may be proposed but genetic counselling must take into account the incomplete penetrance of the gene of 85 % [49]. In late onset hereditary forms [43], genetic counselling is more difficult because asymptomatic carriers have been reported after 70 years [56] and at the present time it is not possible to predict when the disease will start.

FAP unrelated to transthyretin

Hereditary amyloid cranial neuropathy is secondary to a single base mutation at nucleotide 654 of the gene coding for gelsolin located on chromosome 9 [25]. Finally, a point mutation on the gene coding for apolipoprotein A1 on chromosome 11 has been found in one family with FAP associated with nephropathy [38].

Diagnosis (Fig. 1)

Until recently, the diagnosis of amyloid neuropathy required nerve biopsy in order to identify characteristic endoneurial deposits. Genetic studies had considerably modified the diagnostic approach of amyloid neuropathies.

Tab. 3 TTR gene mutations described in association with familial amyloid polyneuropathy.

Exon	Amino-acid	Variant TTR
2	4–47	Cys10 Arg, Leu12Pro[1], Asp18Glu, Pro24Ser, **Val30Met[2]**, Val30Ala, Val30Leu, Phe33Ile, Phe33Val, Arg34Thr, Lys35Asn, Asp38Ala, Glu42Gly, Glu42Asp, Phe44Ser, Ala45Asp, Gly47Arg, Gly47Ala, Gly47Val
3	48–92	Thr49Ile, Ser50Arg, Ser50Ile, Ser52Pro, Glu54Gly, Glu54Lys, Leu55Arg, Leu58Arg, Thr59Lys, Thr60Ala[3], Glu61Lys, Phe64Leu, Lys70Asn[4], Val71Ala[4], Ser77Tyr[3], Ser77Phe, Glu89Gln, Glu89Lys, Ala91Ser
4	93–127	Ala97Gly, Ile107Val[4], Ser112Ile, Tyr114Cys, Tyr116Ser, Ala120Ser, DVal122

[1] associated leptomeningeal amyloidosis.
[2] most common variant in the world, responsible for the disease in Portugal, main endemic area of FAP and in Sweden.
[3] severe associated cardiomyopathy.
[4] inaugural carpal tunnel syndrome.
D: trinucleotide deletion of TTR gene.

Patients with a family history of FAP

In patients with a polyneuropathy and a positive family story of FAP, genetic studies had replaced the nerve biopsy. In Portugal, detection of a point mutation of second exon of TTR gene establishes the diagnosis [53]; in other countries, other TTR gene mutations may be identified by TTR gene sequencing [43].

Patients with seemingly sporadic amyloid polyneuropathy

In the absence of a positive family story, some biological investigations are useful for classification of the neuropathy because specificity of immunolabeling of amyloid deposits is poor. Immunofixation electrophoresis of serum and urine may detect a monoclonal immunoglobulin or light chain in 75% of patients with immunoglobulin light chain amyloidosis (AL) at referral [2]. M protein is various including IgG, IgM, IgA or only light chains [2]. Monoclonal light chains are usually only detected in urine and may be initially absent. In the absence of monoclonal protein, TTR gene analysis is required looking for a TTR gene mutation that might link them to FAP [36, 43].

Genetic studies have other major implications for genetic counselling, presymptomatic diagnosis in their families and prenatal diagnosis for families with early onset [3].

CSF examination may be normal or may show high protein content with albuminocytological dissociation with sometimes protein levels greater than 1 g/L.

Treatment

Symptomatic treatment

Symptomatic treatment has an important place in the care of patients with amyloid neuropathy. Paresthesiae and distal burning pains may be reduced by low doses of clonazepam or association of imipramine-levomepromazine, respectively. In lancinating pains, carbamazepine may be tried. Physiotherapy is required in patients with motor involvement. Symptomatic orthostatic hypotension may be corrected by high doses of dihydroergotamine, 9 alphafluorohydrocortisone or by midocrine. The use of elastic stockings and fractionation of meals during the day may also be useful. Carpal tunnel syndrome may favourably respond to division of flexor retinaculum [47]. In chronic urinary retention, catheterisation should be considered to avoid urinary infection and deterioration of renal function. If an antidepressive treatment is necessary, one must take care in prescribing tricyclic antidepressive which can worsen orthostatic hypotension and urinary disorders. Treatment of associated non neurological manifestations is also important including treatment by pacemaker of severe cardiac conduction disturbances [8] and hemodialysis in severe renal insufficiency.

Specific treatment

There are many potential approaches for the treatment of amyloidosis (*Fig. 2*). The main one consists of suppressing the precursor cells of amyloidogenic proteins and depends of biochemical variety of amyloidosis.

Familial amyloidotic polyneuropathy: Plasma exchanges have been proposed in FAP in order to remove

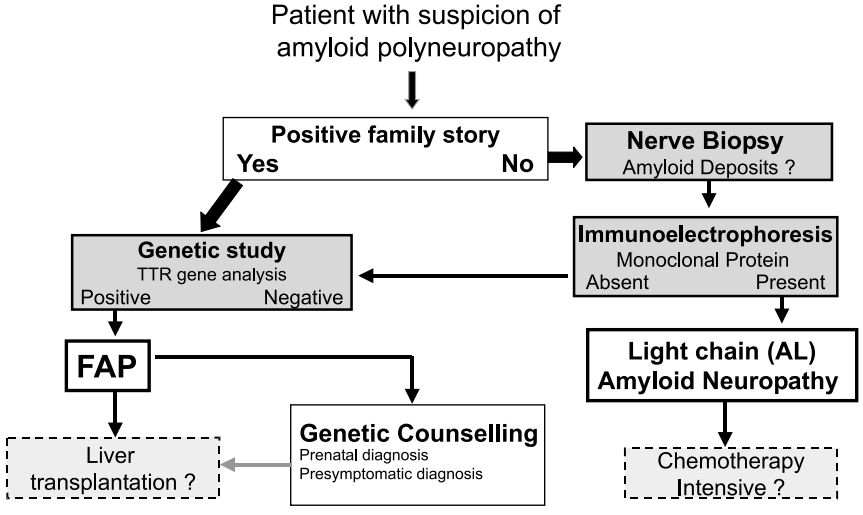

Fig 1 Management of patient with suspected amyloid neuropathy.

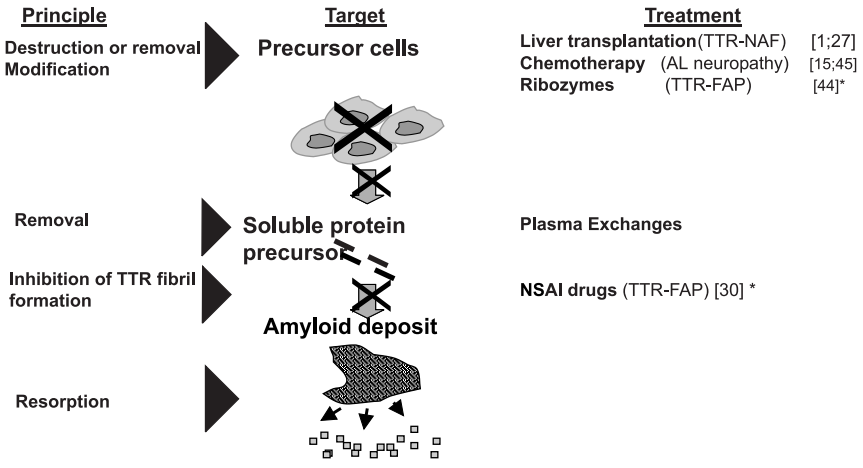

Fig. 2 Amyloid neuropathy: specific therapeutic strategies.

TTR-FAP: transthyretin related familial amyloid polyneuropathy.
AL: light chain.
NSAI: nonsteroidal antiinflammatory drugs.
*: only in vitro studies.

amyloidogenic protein from serum and to reduce amyloid deposition in tissues. Failure of this approach may be explained by the short half-life of TTR which is 2 days [4].

Liver transplantation: Liver transplantation (LT) has been recently proposed as a treatment of TTR-related FAP [27] in order to stop synthesis of amyloidogenic variant TTR and the disease. Liver represents the main source of systemic TTR synthesis [29] as shown by the dramatic reduction of 95% of serum abnormal TTR level in the patients with FAP who received LT [1, 26].

Results

Preliminary results in the first patients operated in Sweden showed dramatic reduction of pretransplant variant TTR in the serum and suggested possible clinical improvement and regression of visceral amyloid deposits by body scintigraphy of P component of amyloidosis [27]. These data have encouraged many centers to propose LT in FAP patients. Although more than 300 FAP patients have been operated around the world, most with met30TTR variant [1, 11, 42, 59, 62], quantitative effects of liver transplantation on the neuropathy after a period longer than 2 years have been rarely reported [1, 11, 62]. Results depend of the stage of the disease at which the treatment is proposed [1, 62]. There is a clinical and electrophysological stability of sensorymotor neuropathy in 76% of patients with moderate neuropathy at the time of LT (i. e. walking unaided) after a mean follow-up 48 months [1]. Furthermore, a marked reduction of axonal loss has been shown by histometric comparative study in 7 operated patients as compared with 4 control FAP patients who did not undergo LT [1]. Improvement of autonomic disturbances initially reported [11, 27] has not been confirmed more recently in patients with a short [60] or long follow-up [1] by non invasive cardiocirculatory autonomic tests. The general condition improved in half the patients, with weight gain[1]. Progression of ocular manifestations reported in FAP after LT could be explained by de novo amyloid synthesis secondary to persistant retinal source of variant TTR [5]. Results of LT in patients with more advanced disease are disappointing with the possibility of progression of the neuropathy [1, 62]. No clear reversal of sensorymotor neuropathy has been demonstrated so far.

Indications

Actual results of LT encourage the use of the operation early in the disease but only in symptomatic patients with proven TTR amyloid neuropathy. LT is contra-indicated in severely affected FAP patients at the time of LT [1, 42] including those with low functional score in the limbs and/or urinary incontinence, as these have been found to be significant and independant risk factors for posttransplantation mortality in a large recent study [1]. Mortality usually occurs within the first year after LT and is secondary to infectious complications favored by poor general condition, neurogenic bladder dysfunction and immunosuppressive therapy [1]. A combined renal and liver transplantation should be discussed for patients with severe renal dysfunction with mild associated neuropathy.

Many questions remain unresolved concerning LT in FAP including the long term benefit of LT, the place of LT in patients older than 60 years, or those carrying non met30TTR gene mutation, sometimes associated with a severe cardiomyopathy [54, 58]. Progression of ventricular wall thickening on serial echocardiography has been reported in these patients [19].

Future prospects

Other therapeutical strategies must be developed for FAP patients because LT is still a major procedure that cannot be proposed to all symptomatic patients as in Portugal where available grafts are lacking or in advanced stages of the diseases or in late onset FAP. A "gene therapy" could be conceivable for correction of variant TTR synthesis of the liver, which is the source of fibril-precursor production. That would require an antisense strategy to specifically block synthesis of variant TTR at DNA or RNA level [44]. As an alternative, new molecules have been recently developed in order to inhibit formation of TTR amyloid fibrils [30].

Immunoglobulin light chain amyloid neuropathy

Chemotherapy has been proposed in order to destroy the plasmacytic secreting clone in immunoglobulin light chain (AL) amyloidosis. Treatment by melphalan and corticosteroids significantly prolonged survival of patients with immunoglobulin light chain amyloidosis as compared wich a group receiving colchicin in a large randomized study [34] and in a subgroup of patients with dominantly neuropathy at referral [45]. Intensive chemotherapy with blood stem cell transplantation has been recently proposed in systemic AL amyloidosis [15] but the effects have yet to be assessed.

Conclusion

Amyloid neuropathies represent the most severe neuropathies in adults and are associated with a poor survival. They are classified in hereditary (FAP) and acquired immunoglobulin light chain (AL) neuropathies. Most of FAP are related to deposits of variant transthyretin (TTR) and are secondary to a point mutation of the TTR gene. TTR gene analysis has modified management of amyloid neuropathies allowing diagnosis of FAP including apparently sporadic cases and genetic counselling with prenatal diagnosis for early onset varieties and presymptomatic detection in their family. Experience of liver transplantation as a treatment of TTR-FAP encourages its use early in the disease.

References

1. Adams D, Samuel D, Goulon-Goeau C, Nakazato M, Costa PMP, Feray C, Planté V, Ducot B, Ichai P, Lacroix C, Metral S, Bismuth H, Said G. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain 2000; 123:1495–504.
2. Adams D, Rerat K, Labauge P, Lacroix C, Said G. Light chain amyloid neuropathies : study of a cohort of 20 patients. J Neurol 1999; 246 : Suppl 1 : I/41.
3. Almeida MR, Alves IL, Sasaki Y, Costa PP, Saraiva MJM. Prenatal diagnosis of familial amyloidotic polyneuropathy: evidence for an early expression of the associated tranthyretin methionin 30. Hum Genet 1990; 80: 623–626.
4. Ando Y, Tanaka Y, Nakazato M, Ericzon BG, Yamashita T, Tashima T, Tashima K, Sakashita N, Suga M, Uchino M, Ando M Change in variant transthyretin levels in patients with familial amyloidotic polyneuropathy type I following liver transplantation. Biochem Biophys Res Commun 1995 ; 211 : 354–8.
5. Ando Y, Ando E, Tanaka Y, Yamashita T, Tashima K, Suga M, Uchino M, Negi A, Ando M. De novo amyloid synthesis in ocular tissue in familial amyloidotic polyneuropathy after liver transplantation. Transplantation 1996 ; 62 : 1037–38.
6. Andrade C. A peculiar form of peripheral neuropathy: familial atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain 1952; 75: 408–427.
7. Antoine JC, Baril A, Guettier C, Barral FG, Convers P, Michel D. Unusual amyloid polyneuropathy with predominantly lumbosacral nerve roots and plexus involvement. Neurology 1991; 41: 206–208.
8. Anzai N, Akiyama K, Tsuchida K, Yamada M, Kito S, Yamamura Y. Treatment by pacemaker in familial amyloid polyneuropathy. Chest 1989; 96: 80–84.
9. Bajada S, Mastaglia FL, Fisher A. Amyloid neuropathy and tremor in Waldenström's macroglobulinemia. Arch Neurol 1980; 37: 240–242.
10. Benson MD, Cohen AS, Brandt KD, Cathcart ES. Neuropathy, M components, and amyloid. Lancet, 1975; 10–12.
11. Bergethon PR, Sabin TD, Lewis D, Simms RW, Cohen AS, Skinner M. Improvement in the polyneuropathy associated with familial amyloid polyneuropathy after liver transplantation. Neurology 1996; 47: 944–951.
12. Brett M, Persey MR, Reilly MM, Revesz T, Booth DR, Booth SE, Hawkins PN, Pepys MB, Morgan-Hughes JA. Transthyretin Leu12Pro is associated with systemic, neuropathic and leptomeningeal amyloidosis. Brain 1999 ; 122 : 183–90.
13. Brown JW, Monroe LS, Palmer L. Intractable vomiting, diarrhea, and orthostatic hypotension in amyloidosis of the peripheral nervous system. Am J Dig Dis 1968; 13: 836–841.
14. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 24–1977. N Engl J Med 1977 ; 296 : 1399–1405.
15. Comenzo RL, Vosburgh E, Falk RH, Sanchorawala V, Reisinger J, Dubrey S, Dember LM, Berk JL, Akpek G, LaValley M, O'Hara C, Arkin CF, Wright DG, Skiner M. Dose-Intensive Melphalan With Blood Stem-Cell Support for the Treatment of AL (Amyloid Light-Chain) Amyloidosis: Survival and Responses in 25 Patients. Blood, 1998 ; 91 : 3662–3670.
16. Coutinho P, Martins Da Silva A, Lopes Lima J, Resende Barbosa A- Forty years of experience with type I amyloid neuropathy. Review of 483 cases. In: Amyloid and amyloidosis Glenner GG, Pinho P, Costa E,Falcao De Freitas A (eds) Amsterdam 1980: Excerpta Medica, pp.88–98.
17. De Freitas FA. The heart in Portuguese amyloidosis. Postgrad Med J 1986; 62: 601–605.
18. Dyck PJ, Lambert EH. Dissociated sensation in amyloidosis. Arch Neurol 1969; 20: 490–507.

19. Dubrey SW, Davidoff R, Skinner M, Bergethon P, Lewis D, Falk RH Progression of ventricular wall thickening after liver transplantation for familial amyloidosis. Transplantation 1997 Jul 15; 64(1): 74–80.
20. Falk RH, Comenzo, RL, Skinner M. Medical Progress: The Systemic Amyloidoses. N Engl J Med 337 (13) ; 1997 : 898–909.
21. Fujimura H, Lacroix C, Said G. Vulnerability of nerve fibers to ischemia. Brain 1991; 114: 1929–1942.
22. Glenner GG, Ignaczak T, Page T. The inherited systemic amyloidosis and localized amyloid deposits. In: Standbury JB, Wyngaarden JB, Fredrickson DS eds. (4th ed.) Metabolic basis of inherited diseases. Mc Graw-Hill. New-York. 1978, pp 1308–1339.
23. Haltia M, Prelli F, Ghiso J, Kiuru S, Somer H, Palo J, Frangione B. Amyloid protein in familial amyloidosis (Finnish type) is homologous to gelsolin, an actin-binding protein. Biochem Biophys Res Com 1990; 167: 927–932.
24. Hanyu N, Ikeda S, Nakadai A, Yanagisawa N, Powell HC. Peripheral nerve pathological findings in familial amyloid polyneuropathy: a correlative study of proximal sciatic nerve and sural nerve lesions. Ann Neurol 1989; 25: 340–350.
25. Hiltunen T, Kiuru S, Hongell V, Helio T, Palo J, Peltonen L. Finnish type of familial amyloidosis: cosegregation of Asp 187Asn mutation of gelsolin with the disease in three large families. Am J Hum Genet 1991; 49: 522–528.
26. Holmgren G, Steen L, Ekstedt J, Groth CG, Ericzon BG, Eriksson S, Andersen O, Karlberg I, Norden G, Nakazato M, Hawkins P, Richardson S, Pepys M. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met 30). Clin Genet 1991; 40: 242–6.
27. Holmgren G, Ericzon BG, Groth CG, Steen L, Suhr O, Andersen O, Wallin BG, Seymour A, Richardson S, Hawkins PN, Pepys MB. Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. Lancet 1993; 341: 1113–6.
28. Izumoto S, Younger D, Hays AP, Martone RL, Smith RT, Herbert J. Familial amyloidotic polyneuropathy presenting with carpal tunnel syndrome and a new transthyretin mutation, asparagine 70. Neurology 1992; 42: 2094–2102.
29. Jacobsson B. In situ localization of transthyretin-mRNA in the adult human liver, choroid plexus and pancreatic islets and in endocrine tumors of the pancreas and gut. Histochemistry 1989; 91: 299–304.
30. Klabunde T, Petrassi HM, Oza VB, Raman P, Kelly JW, Sacchettini JC. Rational design of potent human transthyretin amyloid disease inhibitor. Nat Struct Biol 2000; 7: 312–21.
31. Kelly JJ, Kyle RA, O'Brien PC, Dyck PJ. The natural history of peripheral neuropathy in primary systemic amyloidosis. Ann Neurol 1979; 6: 1–7.
32. Kelly JJ, Kyle RA, Miles JM, O'Brien PC, Dyck PJ. The spectrum of peripheral neuropathy in myeloma. Neurology 1981; 31: 24–31.
33. Kiuru S Familial amyloidosis of the Finnish type (FAF). A clinical study of 30 patients. Acta Neurol Scand 1992 86(4): 346–53.
34. Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, Therneau TM. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997; 336: 1202–7.
35. Meretoja J. Familial systemic paramyloidosis with lattice dystrophy of the cornea, progressive cranial neuropathy, skin changes and various internal symptoms: a previously unrecognized heritable syndrome. Ann Clin Res 1969; 1: 314–324.
36. Misu K, Hattori N, Nagamatsu M, Ikeda Si, Ando Y, Nakazato M, Takei Yi, Hanyu N, Usui Y, Tanaka F, Harada T, Inukai A, Hashizume Y, Sobue G. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan. Clinicopathological and genetic features. Brain 1999; 122: 1951–62.
37. Nichols WC, Dwulet FE, Liepnieks J, Benson MD. Variant apolipoprotein AI as a major constituent of a human hereditary amyloid. Biochem Biophys Res Commun 1988; 156: 762–768.
38. Nichols WC, Gregg RE, Brewer B, Benson MD. A mutation in apolipoprotein A-I in the Iowa type of familial amyloidotic polyneuropathy. Genomics 1990; 8: 318–323.
39. Nick J, Contamin, Brion S, Guillard A, Guiraudon M. Macroglobulinémie de Waldenström avec neuropathie amyloïde. Observation anatomo-clinique. Rev Neurol (Paris) 1963; 109: 21–30.
40. Niklasson U, Olofsson BO, Bjerle P. Autonomic neuropathy in familial amyloidotic polyneuropathy. A clinical study based on heart rate variability. Acta Neurol Scand 1989; 79: 182–7.
41. Olofsson BO, Andersson R, Furberg B. Atrioventricular conduction in familial amyloidosis with polyneuropathy. Acta Med Scand 1980; 208 : 77–80.
42. Parrilla P, Ramirez P, Andreu LF, Bueno SF, Robles R, Miras M, Acosta F, Viader-Farre D, De Mingo P, Bermejo J, Garrido SFJ, Munar-Ques M. Long-term results of liver transplantation in familial amyloidotic polyneuropathy type I. Transplantation 1997; 64 : 646–9.
43. Plante-Bordeneuve V, Lalu T, Misrahi M, Reilly MM, Adams D, Lacroix C, Said G Genotypic-phenotypic variations in a series of 65 patients with familial amyloid polyneuropathy. Neurology 1998; 51(3): 708–14.
44. Propsting MJ, Blaschke M, Haas RE, Genshel J, Hedrich HJ, Manns MP, Schmidt HH. Inosine (15.1) hammeared ribozymes for targeting the transthyretin–30 mutation. Biochem Biophys Res Com 1999 ; 260 : 313–17.
45. Rajkumar SV, Gertz MA, Kyle RA. Prognosis of patients with primary systemic amyloidosis who present with dominantly neuropathy. Am J Med 1998 ; 104 : 232–7.
46. Reilly MM, Adams D, Davis MB, Said G, Harding AE.Haplotype analysis of French, British and other European patients with familial amyloid polyneuropathy (met 30 and tyr 77). J Neurol 1995; 242: 664–8.
47. Rukavina JG, Block WD, Jackson CE, Falls HF, Carey JH, Curtis AC Primary systemic amyloidosis: a review and an experimental, genetic, and clinical study of 29 cases with particular emphasis on the familial form. Medicine 1956 Jan; 72(1): 45–63.
48. Said G, Ropert A, Faux N. Length-dependent degeneration of fibers in Portuguese amyloid polyneuropathy: a clinicopathologic study. Neurology 1984; 34: 1025–32.
49. Sakoda S, Suzuki T, Higa S Ueji M, Kishimoto S, Hayashi A, Yasuda N, Takaba Y, Nakajima A. Genetic studies of familial amyloid polyneuropathy in the Arao district of Japan. I: The genealogical survey. Clin Genet 1983; 24: 334–38.
50. Sales-Luis ML. Electroneurophysiological studies in familial amyloid polyneuropathy portuguese type. J Neurol Neurosurg Psychiatry 1978; 847–850.
51. Saraiva MJM, Birken S, Costa PP, Goodman DS. Amyloid fibril protein in familial amyloidotic polyneuropathy, Portuguese type. J Clin Invest 1984 ; 74 : 104–119.
52. Saraiva MJM. Transthyretin mutations in health and disease. Hum Mut 1995; 5: 191–196.

53. Sasaki H, Sakaki Y, Matsuo H, Goto I, Kuroiwa Y, Sahashi I, Takahashi A, Shinoda T, Isobe T, Takagi Y. Diagnosis of familial amyloid polyneuropathy by recombinant DNA techniques. Biochem Biophys Res Commun 1984; 125: 636–642.
54. Satier F, Nichols WC, Benson MD. Diagnosis of familial amyloidotic polyneuropathy in France. Clin Genet 1990; 38: 469–473.
55. Schenone A, Primavera A, De Martini I, Bianchini D, Mancardi GL. Amyloid neuropathy in light chain multiple myeloma. Clin Neuropathol 1989; 8: 156–157.
56. Sequeiros J, Saraiva MJM. Onset in the seventh decade and lack of symptoms in heterozygotes for the TTR^{Met30} mutation in hereditary amyloid neuropathy type I (portuguese, andrade). Am J Med Genet 1987; 27: 345–357.
57. Shirahama T, Cohen AS. High resolution electron microscopic analysis of the amyloid fibril. J Cell Biol 1967; 33: 679–708.
58. Staunton H, DerVan P, Kale R, Linke RP, Kelly P. Hereditary amyloid polyneuropathy in north west Ireland. Brain 1987; 110: 1231–1245.
59. Suhr OB, Holmgren G, Steen L, Wikstrom L, Norden G, Friman S, Duraj FF, Groth CG, Ericzon BG. Liver transplantation in familial amyloidotic polyneuropathy. Transplantation 1995; 60: 933–938.
60. Suhr OB, Wiklund U, Ando Y, Ando E, Olofsson BO. Impact of liver transplantation on autonomic neuropathy in familial amyloidotic polyneuropathy : an evaluation by spectral analysis of heart rate variability. J Int Med 1997; 242: 225–229.
61. Takahashi K, Shigehiro YI, Kimura Y, Araki S. A clinicopathologic, histochemical, immunohistochemical, and ultrastructural study. Human Pathol 1991; 22: 519–527.
62. Takei Y, Ikeda SI, Hashikura Y, Ikegami T, Kawasaki S. Partial liver transplantation to treat familial amyloid polyneuropathy : follow-up of 11 patients. Ann Intern Med 1999; 131: 592–595.
63. Thomas PK, King RHM. Peripheral nerve changes in amyloid neuropathy. Brain 1974; 97: 395–406.
64. Traynor AE, Gertz MA, Kyle RA. Cranial neuropathy associated with primary amyloidosis. Ann Neurol 1991; 29: 451–454.
65. Uemichi T, Liepnieks JJ, Benson MD. A trinucleotide deletion in the transthyretin gene (delta V 122) in a kindred with familial amyloidotic polyneuropathy. Neurology 1997; 48 (6) : 1667–70.