Artículo especial

Malnutrition, pharmaconutrition and other considerations in AL amiloidosis, a rare disease with masquerading symptoms and usually delayed diagnosis

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Abstract

Amyloid Light-chain (AL) amyloidosis is a very rare disease. Nutritional and pharmaconutrional aspects are described. Nutrition repletion of malnourished AL patients is an essential strategy for improving treatment efficacy and clinical outcomes. Early diagnosis of AL amiloidosis is difficult to establish due to the fact that signs and symptoms appearing mimic other processes that delay the final correct histological diagnosis. Untreated patients with this disease have a dismal outcome, with a median survival of 10-14 months from diagnosis. The sooner the treatment is established the better the results are. Modern chemotherapeutical agents, based primarily in cyclophosphamide, bortethomid and dexametasone, produce a rapid, deep, and durable response in the majority of patients. Autologous stem cell transplantation remains restricted to selected patients who are generally without advanced cardiac amyloidosis.

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Key words: *AL amyloidosis. Cardiac amyloidosis.*

MALNUTRICIÓN, FARMACONUTRICIÓN Y OTRAS CONSIDERACIONES EN AMILOIDOSIS AL, UNA ENFERMEDAD RARA CON SÍNTOMAS EQUÍVOCOS Y RETRASO HABITUAL EN EL DIAGNÓSTICO

Resumen

La amiloidosis de cadenas ligeras (amiloidosis AL) es una enfermedad muy rara. En este artículo se describen los aspectos nutritivos y farmaconutritivos de la enfermedad. La renutrición de los pacientes con amiloidosis malnutridos es una estrategia esencial para mejorar la eficacia del tratamiento y el resultado a largo plazo. El diagnóstico precoz de la amiloidosis AL es difícil, debido a que los signos y síntomas que aparecen emulan otras entidades morbosas y retrasan el correcto diagnóstico histológico final. Los pacientes no tratados tienen un porvenir oscuro, con una supervivencia media de entre 10 y 14 meses desde el diagnóstico. Cuanto antes se establezca el tratamiento, mejores son los resultados. Los agentes quimioterapéuticos modernos, en concreto ciclofosfamida, bortezomid y dexametasona, producen una respuesta rápida, importante y duradera en la mayoría de los pacientes. El trasplante de células autólogas debe restringirse a un grupo selecto de pacientes sin enfermedad cardiaca avanzada secundaria a la amiloidosis.

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Palabras clave: *Amiloidosis AL. Amiloidosis cardiaca.*

Introduction

Amyloid Light-chain (AL) amyloidosis is a very rare disease. Antibody-producing cells do not function properly and ellaborate abnormal protein fibers made of components of antibodies called light chains. These light chains come together to form amyloid deposits in multiple organs which can cause serious damage. Al amyloidosis must always be confirmed histologically. A biopsy specimen should stain positively with Congo red and demonstrate apple-green birefringence under polarized light.

Untreated patients with this disease have a dismal outcome, with a median survival of 10-14 months from diagnosis[1].

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Report of one case

Sixty seven year old white Caucasian male. No known allergies. No toxic habits. No familial history of hematological disorders.

Personal history

– Pharmacology treated arterial hypertension, since 8 years before.
– Mild hyperuricemia; no treatment necessary.
– Megacolon. Chronic constipation.
– Surgical operations: tonsillectomy at 30 y.o. Anal fissure 8 years ago. Right carpal tunnel syndrome surgically released in August 30/2013. Mild improvement.
– Present treatment: Dexametasone, aciclovir 800/day, septrim, lanzoprazol, amiodarone, sintrom, furosemid 20 mg/d, spironolactone and zolpiden . Green tea regularly.

Present disease

The patient suffers paresthesias in both hands since January 2013, being diagnosed bilateral carpal tunnel syndrome, with right predominance. Progressive dyspnea during the last six months with dry cough; (dyastolic disfunction in EKG) and auricular flutter (Nov 2013). Blood pressure normalized, not needing pharmacological treatment any more. Weight loss of 8Kg, erectile malfunction, and voice changes. No orthostatic hypotension, ortopnea or nocturnal paroxysmal dyspnea. No diarrhea, (Chronic constipation).

Laboratory findings

Blood: creatinine 0.8 mg/dl; normal liver biology (included Alk. Phosphatase); total proteins 63g/L. Serum proteogram with small beta band (13%); albumin 37 g/L. Serum immune fixation: Bence Jones kappa type protein. Free serum light chains: 6800 mg/L, lambda 8,3mg/L; ratio 816. Normal blood coagulation (Quick time 90%) Urine analysis: proteins: 600 mg/24 hours composed of light chains. Urine immune fixation: Bence Jones kappa type. Medullar biopsy: 10-15% plasma cells (aberrant phenotype, kappa restriction). Negative red Congo stain. In FISH study, numerical and structural alteration of ATM gen (11q22) in 12% of analyzed cells (600). Abdominal fat biopsy: no evidence of abdominal amyloid deposits (a second abdominal biopsy performed three weeks later in another institution gave positive results). Rectal biopsy: Inflammatory changes and stromal changes, red Congo positive.

Cardiological study

Troponin I: 0.11 ng/mL (Normal values < 0.08) NT pro BNP: 3570 pg/ml (NV <125). EKG: sinusal arrhythmia, low voltage in extremities and poor voltage in precordial area.(Fig 1) Echocardiogram: Left ventricle with slight increase in septal width (13 mm) concentrically with back wall. Ejection Fraction (EF) 60%. Aortic, mitral and tricuspid valves slightly thickened. Slight biauricular dilatation. (Fig. 2).

Cardiac magnetic resonance (MR): concentric myocardial hypertrophy with septal predominance (14 mm). EF: 64%; slight biauricular dilatation; slight pericardial effussion, compatible with cardiac amyloidosis. (Figs. 3-5).

Several auricular fibrillating episodes needing electric cardiac cardio version in two occasions, (catheter ablation radiofrequency of the tricuspid cV isthm) and, finally, bicameral definitive pacemaker implanted (St
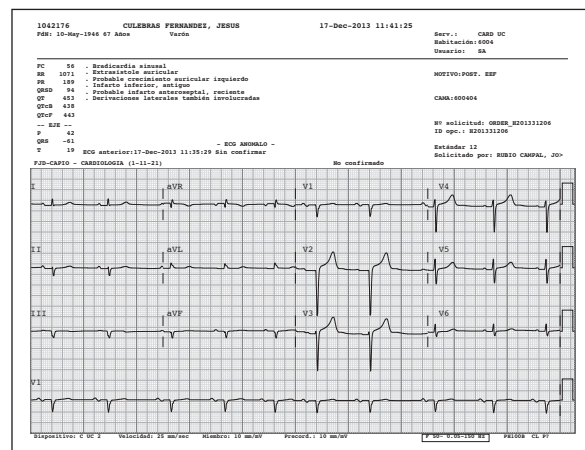

Fig. 1.—ECG shows low voltages in the QRS complexes and pseudo infarct; pattern typical of amyloidosis.
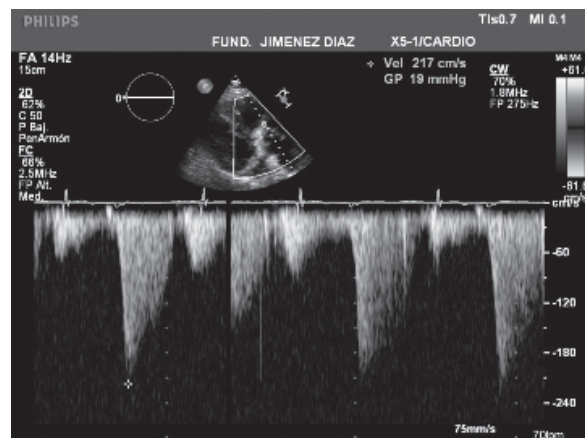

Fig. 2.—The echocardiogram showed moderate concentric hypertrophy (septum thickness 13 mm), pattern of diastolic dysfunction (pseudo normal wave pattern), and moderate biauricular enlargement. No evident granular sparkling of the myocardium was visible.
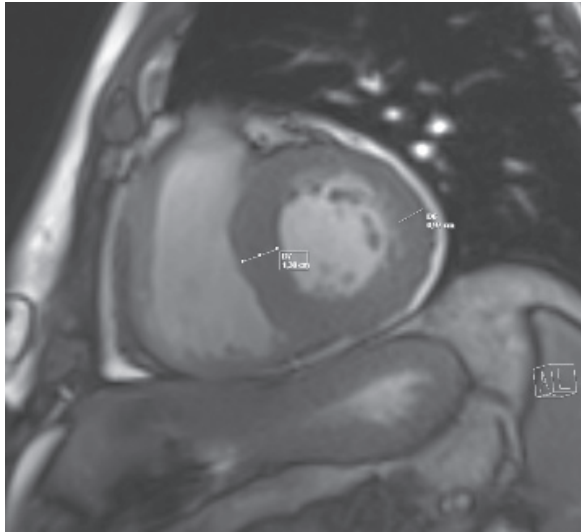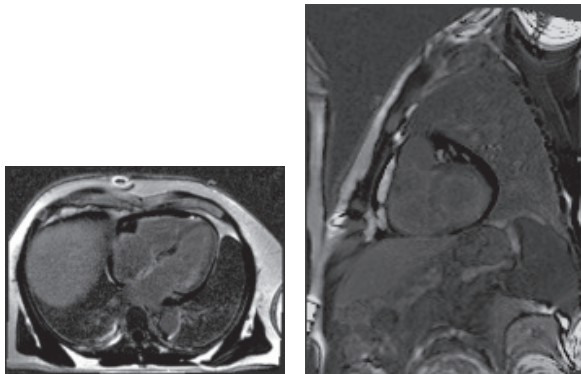
Fig. 3.—Magnetic Resonance Imaging. Short axis, basal and medial level, showing concentric hypertrophy (septum 13,8 mm) and minimal pericardial effusion.

Figs. 4a and b.—Late gadolinium enhancement (LGE), four chambers and short axis. Late gadolinium enhancement shows difficulties in finding the correct inversion time with characteristic global, subendocardial LGE with slight hypertrophy (maximum wall thickness in this case was 13.8 mm).
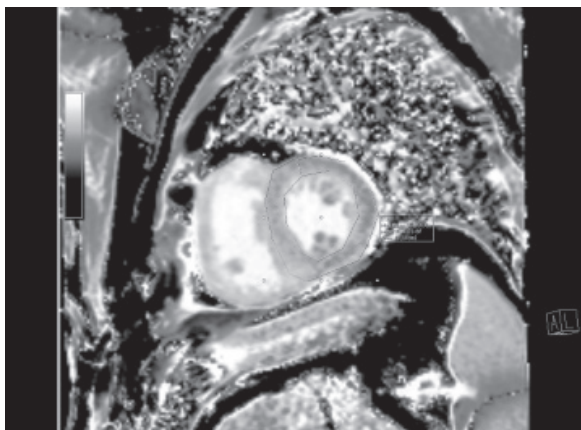

Fig. 5.—Short axis T1 mapping was performed without contrast administration. Myocardial T1 was significantly elevated compared to normal subjects.

Jude Accent DR MR en DDDr 70-120 lpm con AV 300 ms) in January 7, 2014.

At present the patient is receiving diuretic treatment, antiarrithmic drug (amiodarone) and anticoagulants.

In Dec 2, 2013 chemotherapy treatment was started, with oral cyclophosphamide, (600 mg, days 1,8 and 15), subcutaneous Bortezomid (1.3 mg/m2, days 1,4,8 and 11) and oral dexametasone (reduced doses from 40 to 20 mg, days 1,4,8 and 11) in cycles of 21 days (CyBorD). Patient completed six cycles. A significant reduction of circulating free kappa light chains was obtained with this treatment (159 mg/L) having acceptable tolerance.

Clinical exploration

Blood pressure: supine 119/79; sitting: 122/89; standing up: 115/77 mmHg. No blood diathesis. Normal tongue. No peripheral adenopathies. CVA: rhythmic tones (patient with pacemaker), No murmurs, Bimaleolar subedemas. Positive jugular ingurgitation 7-8 cm. Subcrepitant noise in left pulmonary base. Abdomen: globulous, painless, liver border palpated in deep inspiration.

Laboratory findings.
(Hospital Clinic I Provincial, Barcelona, December 17, 2013)

Normal biochemistry, included creatinine and alkaline phosphatase; slight hipertriglicemia. TGP 45 U/L. GGT 164U/L. Total proteins 62g/L. Serum proteogram without band. Seric immune fixation: restricted motility component constituted by IgC-kappa, monoclonal nature. Urinary protein: 141mg/24h. Urine immune fixation: restricted motility component detected, constituted by free kappa light chains; monoclonal nature. Troponin I: 0.081 ng/mL (Reference values <0.050). BNP 326 pg/mL (Ref. values 4-37) Normal hemogram, except for slight neutrofilic leucocitosis. GSR 8 mm/h. Quick time 29% (Treatment with warfarin; factor X: 19U/dL (Reference values 65-135) Negative serology for HIV, HBV and HCV. Normal thyroid profile. IgM dossification: <0.16 g/L (RV 0.36-2.61) IgA: normal, IgG 6.1 g/L (RV 6.8-15.3) Free kappa light chains in serum: 110 mg/L (RV 3.3-19.4), lambda: 2.94 mg/L (RV 5.71-26.3); ratio 37. PAAF of subcutaneous fat: amyloid deposits (Red Congo positive)

Complementary explorations

Echocardiogram: compatible with restrictive miocardiopathy. Moderately hypertrophic left ventriculum (SIVtd 14 mm), non dilated; normal global motility. Ejection Fraction (EF) 65%. Diastolic function not evaluable due to bicameral pacemaker rhythm, but

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with restrictive type alterations. Mild mitral insufficiency. Enlarged valves with normal motility. Mild aortic insufficiency, with normal opening. Slightly dilated right ventricle, not hypertrophied, with normal global motility. Slight tricuspid insufficiency. Enlarged veils with slightly restricted motility. Normal systolic pulmonary arterial pressure (estimated 32mmHg) Moderate right atrial dilatation and slight left atrial dilatation. Inferior vena cava slightly dilated with normal inspiratory collapse.

Pacemaker electrodes in right cavities. Slight pericardial effusion.

To summarize, this is a 67 y.o patient with recent diagnosis of light chain kappa amylidosis, with cardiac (Functional class II, Mayo cardiac stage III) soft tissue (carpal tunnel syndrome) and digestive (Rectum positive Congo red) involvement. Following six cycles with CyBorD the response is excellent, with adequate tolerance. The patient had a "very good partial response". For this reason further treatment with six cycles with cyclofosfamide (650 mg/m2 every 4 weeks) and prednisone (30 mg every other day) were conducted until September 2014. Intensification of the treatment with autologous stem cell transplantation (ASCT) and melfalan 200 mg was disregarded. . Cardiac staging has been reevaluated by means of biomarkers in serum, echocardiogram and cardiac MR.

Early dyagnosis of al amyloidosis

Early diagnosis of AL amiloidosis is difficult to establish due to the fact that signs and symptoms appearing mimic other processes that delay the final correct histological diagnosis. Every effort must be made towards early detection and diagnosis of AL amyloidosis. There is a direct correlation between early diagnosis and better clinical outcome.(Table I)

Pharmacological treatment

Pharmacological treatment of AL amiloidois is based primarily in cyclophosphamide, bortethomid and dexametasone. This combination (CyBorD) produces a rapid, deep, and durable response in the majority of patients with AL, even in the setting of cardiac and multiorgan impairment . Given the time delays of stem cell transplantation, CyBorD may be the fastest and most effective regimen to be reported[2].

Conventional chemotherapy and intensive treatment with stem cell transplantation

Several studies have shown the efficacy of high-dose dexamethasone-based regimens in inducing haematological responses and prolonging survival. Impressive efficacy, with > 60% haematological response, has been reported with melphalan-dexamethasone regimens[3] with median survival up to 5 years. In experienced centers, intensive treatment and ASCT obtains a similar haematological response rate[4]. ASCT remains restricted to selected patients who are generally without advanced cardiac amyloidosis. In 2007, a French multicentre randomized prospective trial showed that, compared with ASCT, melphalan-dexamethasone had similar efficacy with less toxicity, resulting in increased survival (22.2 months in the ASCT group and 56.9 months in the group with oral melphalan-dexamethasone; $P = 0.04$). A recent study by Cibeira et al[5] showed that treatment of selected AL patients with high-dose melphalan and autologous stem cell transplantation resulted in a high organ response rate and long overall survival, even for those patients who did not achieve complete response.

Whereas ASCT is still commonly used in the USA in patients without severe disease, it is no longer used in most European countries, except Germany. Melphalan-dexamethasone has become the first-line treatment in France for the majority of patients[3].

The proteasome inhibitor bortezomib, a relatively novel chemotherapeutical agent, is offering a much larger percentage of complete and partial remissions. Bortezomid with cyclophosphamide and dexamethasone is showing good tolerance and impressive response rates. This combination, due to its very rapid efficacy, is now the treatment of choice for primary AL amyloidosis

Warfarin anticoagulation

Unless major contraindications exist, the presence of atrial fibrillation in AL amyloidosis is a very strong indication for warfarin anticoagulation because of a very high rate of thromboembolic events. In severe cardiac amyloidosis, the atrium is infiltrated, and dysfunctional and atrial thrombi may be present even during sinus rhythm. It is therefore prudent to anticoagulate patients with AL amyloidosis even if they are in sinus rhythm if there is a small transmitral A wave seen on transthoracic echocardiography (_20 cm/s)[6].

Malnutrition in AL amyloidosis

Malnutrition is associated with changes in body composition, delayed wound healing, decreased functional capacity, impaired immune function, changes in the different organ systems and intolerance to medical treatment or surgical interventions[7]. Malnutrition leads to sarcopenia. The concept of sarcopenia implies loss of muscle mass and function. It is a condition that accompanies aging, although it not always has clinical consequences. It is produced by many factors: nervous system (loss of alpha motor units in the spinal cord), muscular (loss of muscle quality and mass), humoral

Table I
Clinical signs and symptoms that could have given the opportunity to make an earlier diagnosis

Date	Symptoms	Consultant	Dyagnosis	Action	Comments
Jan 6/2013	Mild finger paresthesias	Neurologist. Informal conversation	Distal paresthesias	Suggested large doses of Vit B (METANX)	*"There are more than 50 causes of distal paresthesias. DM, metabolic syndrome, hypothiroidismm…"*
June 2013		Neurologist. Informal conversation	Bilateral finger paresthesias	None	*"Functional symptoms"*
August 2013	Bilateral finger paresthesias and loss of sensitivity	Electromyography	Bilateral medial impairment. Right sural impairment	Recommend carpal tunnel decompression	*"Very common at 67 years old"*
September 2013	Carpal tunnel syndrome	Plastic Surgery		Right carpal decompression	*Operation uneventful.* *"Symptoms take several months to subside."*
September 2013	Progressive muscle weakness. Lack of elasticity down slope	Informal conversation with colleagues	Overweight. Age 67	Loose weight	
October 2013	Dry cough	ENT	Mild gastro esophageal reflux.	Laringoscopy	
November 2013	Progressive heart insufficiency, especially upslope	Cardiologist	Diastolic malfunction. Fevi 55% Low voltage		*Mild alterations normal at 67 y.o*
November 2013	Diastolic malfunction	Radiologist	TC and MR alterations, suggestive of amyloidosis. Light chain proteins in blood and urine	Fat biopsy. Rectal biopsy, Bone marrow biopsy, cardiac TC, cardiac MR, blood and urine analytics	*Check with Hematology*
November 2013	Amyloidosis?	Hematology	Histologically proven AL Amiloidosis	Start treatment CyBorD	

(decrease in anabolic hormones such as testosterone, estrogens, GH and increase of several interleukins), and life style (physical activity). The main clinical consequences of sarcopenia relate with functional independence. Thus, the sarcopenic patient has greater difficulty walking, or does it more slowly, climbing up stairs, or doing basic daily living activities. These difficulties increase the risk for falls and fractures. They also affect bone formation, glucose tolerance, and body temperature regulation. Besides, dependency is a mortality risk factor.

Malnourished patients are at risk of experiencing infectious and cardiorespiratory complications[8,9], increased morbidity and mortality and prolongation of hospital stay. Nutritional intervention is essential, including patients with good previous nutritional status, since the worsening of nutritional status due to critical illness will be a determinant factor of poor subsequent outcome[10].

AL amyloidosis is often diagnosed at an advanced stage, when treatment perspectives are limited or patients are less likely to tolerate chemotherapy. Nutrition status should be systematically evaluated in AL with simple and objective measurements. Malnutrition at diagnosis of AL amyloidosis is a frequent comorbidity and an independent predictor of mortality The prognostic value of nutrition status becomes evident approximately 4-6 months after diagnosis, when treatment response can be expected. Future research may demonstrate that nutrition repletion of malnourished AL patients is an essential strategy, including those with good previous nutritional status, for improving

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Table II
Timing between clinical suspicion, diagnosis and treatment in the clinical case described

Date	Action	Comments
Nov/21/2013	Echocardiogram Subcutaneous abdominal fat biopsy	Amyloidosis to be ruled out
Nov/27/2013	Blood and urine analysis, echocardiogram, rectal biopsy, bone marrow biopsy, heart MR, heart TC. Clinical consultation with Internal Medicine and with haematology	Clinical determinations to rule out amyloidosis
Nov 28/2013	Light chain elevated 6800 mg/L. Red Congo staining positive in rectal biopsy	Primary amyloidosis confirmed
Dec 2/2013	First cycle CyBorD started	First Cycle well tolerated and completed dec 12
Dec 23/2013	Second cycle CyBorD started	Second Cycle well tolerated and completed Jan 2, 2014
Jan 1/2014	Third CyBorD cycle started	

Table III
Differential dyagnosis of amyloidosis

- Idiopathic peripheral neuropathy
- Bilateral distal progressive paresthesia
- Carpel tunnel syndrome
- Automatic nervous system involvement: syncope, erectile dysfunction, gastroparesis, and diarrhea. gastric-emptying disorder, pseudo-obstruction, voiding dysfunction
- Nephrotic-range proteinuria, with or without renal insufficiency
- Heart failure or fatigue secondary to restrictive cardiomyopathy
- Echo: mean wall thickness> 12 mm, no other cardiac cause
- Unexplained hepatomegaly
- unexplained voice changes (larynx)
- Soft-tissue involvement : tongue enlargement, submandibular swelling, recurrent periorbital purpura, amyloid lymphadenopathy, claudication of the limbs or jaw
- Clinical Arthropathy
- Myopathy by biopsy or pseudohypertrophy
- Lung: Interstitial radiographic pattern

treatment efficacy and clinical outcomes[11]. In AL amyloidosis, malnutrition at diagnosis is a frequent co morbidity that affects the prognosis independently of hematologic response to treatment and cardiac stage. Nutrition status should be systematically considered in future intervention trials in AL amyloidosis. Nutrition support trials are warranted.

Pharmaconutrition; functional food

It has been demonstrated, or at least suspected in many instances, that specific nutrients do play a role in nutritional metabolic support. Glutamine, argine, ω-3 fatty acids, and RNA have shown beneficial effects postoperatively following abdominal surgery through the beneficial effect of pharmaconutrition in wound healing and in reduction in suture dehiscences. Given the essential action of micronutrients (vitamins, trace elements) in maintaining immune and antioxidant system function, their supply is necessary in any patient susceptible to these deficiencies, even if of subclinical type. In some instances certain micronutrients or antioxidants exert a proven or suggested specific effect and therefore should be recommended[12]

A food can be regarded as "functional" if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either the state of well-being and health or the reduction of the risk of a disease. The beneficial effects could be either maintenance or promotion of a state of well-being or health and/or a reduction of the risk of a pathologic process or a disease.

Green tea contains an active polyphenol called Epigallocatechin Gallate (EGCG). Consumption of EGCG in patients with cardiac involvement with AL amyloidosis apparently causes a significant decrease in left ventricular wall thickness and mass, as well as an improvement in NYHA functional classification and left ventricular ejection fraction.

Green tea might be useful to diminish cardiac amyloid deposits and improve function in AL amyloidosis. The effects of dietary supplement with epigallocatechin gallate (EGCG) are currently in progress. The end point of these studies is to clarify if EGCG causes a significant decrease in left ventricular wall thickness and mass, as well as an improvement in NYHA functional classification and left ventricular ejection fraction.

A Phase II open-label randomized study of dietary supplement with epigallocatechin gallate (EGCG) to improve cardiac dysfunction in patients with AL amyloidosis is being conducted in Pavia, Italy. The

Table IV
Organs potentially involved in AL (primary) amyloidosis

- Heart
- Kidneys
- Liver
- GI system
- Nervous system

Table V
Hematologic (Immunochemical) Response Criteria

- **Complete response (CR)**
  Serum and urine negative for a monoclonal protein by immunofixation
  Free light chain ratio normal
  Marrow< 5% plasma cells

- **Partial response (PR)**
  Serum M component> 0.5 g/dL, a 50% reduction
  Light chain in the urine with a visible peak and >100 mg/day and 50% reduction
  Free light chain>10 mg/dL (100 mg/L) and 50% reduction

- **Progression From CR**
  Any detectable monoclonal protein or abnormal free light chain ratio (light chain must double)

- **From PR or stable response**,
  50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day;
  A visible peak must be present
  Free light chain increase of 50% to>10 mg/dL (100 mg/L)

- **Stable**
  No CR, no PR, no progression

recruitment period of this study is being conducted at this time. Therefore results will not be available until at least 2016[13].

Cardiac complications of myocardial amyloid fibril deposition

An update in diagnosis and management of cardiac amyloidosis has been published by Mohty et al[14]. Symptoms are non-specific: dyspnoea due to heart failure, syncope, vertigo due to rhythm or conduction disorders and, rarely, chest pain. This is the reason why diagnosis is delayed (Tables I-IV). Cardiac involvement may have many serious consequences: severe congestive heart failure with initially preserved LVEF and decreased LV compliance due to amyloid deposit, and advanced diastolic dysfunction; decreased LVEF may follow diastolic dysfunction, leading to terminal and fatal heart failure; chronic elevated LV filling pressure leads to left atrial enlargement then to paroxysmal or persistent atrial fibrillation; atrial thrombi are frequent in cardiac amyloidosis, even in patients with sinus rhythm, and can cause systemic embolic events;

non-sustained or sustained ventricular arrhythmias are also potential complications of cardiac amyloidosis; conduction disturbances are prevented and treated by pacemaker implant; orthostatic hypotensive episodes are due to autonomic dysfunction and/or neurovegetative involvement or have a hypovolemic cause; severe dysautonomia can cause syncope and hypotensive cardiac treatment (angiotensin-converting enzyme inhibitors) should be avoided in these patients; autonomic dysfunction can be also expressed by the loss of heart variability; indeed, an SDNN < 50 ms on a 24-hour Holter ECG was found to be an independent predictor of short-term mortality in AL patients[15]; chest pain may occur in rare cases where amyloid deposits affect the microcoronary circulation, whereas the macrocoronary vessels are usually free of significant stenosis[16].

EKG disturbances in AL amyloidosis

Electrocardiograms (ECGs) are abnormal in 90% of cases with cardiac involvement. The largest study that reported ECG findings consisted of 127 patients with AL and biopsy-proven cardiac involvement[17]. The study confirmed that the two most common abnormalities were low voltage QRS complex (defined as all limb leads < 5 mm in height) and a pseudo infarct pattern on the precordial leads which were seen in roughly 50% of the patients included. Right and left bundle branch block are uncommon. Other changes that may occur include conduction abnormalities (such as second and third degree atrioventricular block), more frequently atrial fibrillation[18] and, rarely, ventricular tachycardia. A fragmented QRS (notches and RsR' pattern in the absence of QRS prolongation) is significantly more frequent in patients with cardiac amyloidosis[19] (Fig. 2).

Cardiac supportive treatment

Apart from specific treatment of the underlying haematological disease, symptomatic treatment and supportive care are necessary in patients with organ failure. Most drugs commonly used for the treatment of congestive heart failure are inefficient or appear to be dangerous in patients with AL amyloidosis[20]. Beta-blockers are deleterious because they decrease heart rate, which is the only mechanism that can maintain cardiac output in this disease; they may also aggravate autonomic dysfunction like angiotensin-converting enzyme inhibitors. Digitalis has been shown to accumulate in cardiac amyloid deposits. For this reason, digitalis is not recommended[21].

Loop diuretics, given at high dosage in patients with severe fluid retention, are the mainstay of management. Amiodarone should be considered as first-line therapy for arrhythmia. Anticoagulation therapy is mandatory in patients with supraventricular arrhyth-

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mia but needs to be discussed in patients with sinus rhythm and severe contractile atrial dysfunction. Pacemaker implantation may be indicated in patients who develop symptoms of bradycardia or conduction disorders. A heart transplant should be considered in selected young patients with advanced amyloid cardiomyopathy free from other comorbidities[22,23].

Prognosis in AL amyloidosis

Survival depends mainly on the extension and severity of organ involvement, particularly the presence of amyloid heart disease, and on the haematological response to therapy. Prognosis is influenced relatively little by the underlying, usually non-proliferating, monoclonal plasma cells, even though bone marrow plasma cell infiltration higher than 10% has been associated with poorer outcome [24]. (Table V).

Only 15 years ago, survival in AL amyloidosis was poor, with a median overall survival of 18 months[25]. Since then, the disease prognosis has been transformed with the development of new strategies that efficiently suppress secretion of amyloid-forming LCs, giving a median survival of > 5 years. Early diagnosis is therefore a critical step to avoid irreversible damage, especially to the heart.

Final considerations and conclusions

AL amyloidosis is a rare disease with equivocal and masquerading symptoms. Delayed diagnosis is a major factor in poor prognosis. Every effort must be made to make the diagnosis earlier. Timely diagnosis is a great concern. Untreated patients with this disease have a dismal outcome, with a median survival of 10-14 months from diagnosis.

Amyloidosis should be ruled out in all patients suffering carpal tunnel syndrome. The societies of Neurology and Neurosurgery should establish this protocol mandatory. Monoclonal protein testing of the serum and urine is readily available and should be performed on all suspected cases. AL amyloidosis is the most common and dangerous form of amyloidosis and definitely should be ruled out. In addition to serum and urine protein electrophoresis and immunofixation, serum free light chain test can increase the sensitivity (especially in monoclonal light chain only cases) by 10%-15%.

AL amyloidosis must be ruled out also in diastolic insufficiency syndrome and in rapidly developing miocardiopathy. A patient with dyspnoea, unexplained fatigue and LV hypertrophy on TTE contrasting with the microvoltage of QRS amplitude should alert the clinician to an infiltrative process rather than a classical sarcomeric hypertrophic or hypertensive cardiomyopathy; in this case it is important to refer the patient to a specialist in internal medicine and/or a hematologist to perform more specific biological and/or genetic testing.

Extracardiac signs, in addition to unexplained LV thickening on echocardiography in the absence of increased voltage on ECG, favour amyloid cardiomyopathy.

The proteasome inhibitor bortezomib, a relatively novel chemotherapeutical agent, is offering a much larger percentage of complete and partial remissions. Bortezomid with cyclophosphamide and dexamethasone is showing good tolerance and impressive response rates. This combination, due to its very rapid efficacy, is now the treatment of choice for primary AL amyloidosis.

Apart from specific treatment of the underlying haematological disease, symptomatic treatment and supportive care are necessary in patients with organ failure.

Unlike other causes of heart failure, supportive treatment is usually very limited and can be dangerous. Despite important developments in chemotherapy for AL, the prognosis of patients with advanced cardiac involvement remains poor. Finally, a variety of novel specific therapies are on the horizon, which can inhibit new amyloid formation and enhance clearance of existing deposits. Patients should be instructed to control water intake, body weight and urine output on a daily basis in order to prevent overloads and subsequent cardiac insufficiency.

Due to the occurrence of severe cardiac complications, ASCT cannot be offered to all diagnosed patients. Aged patients, i.e. 65 years old or more, should be critically evaluated for transplantation. ASCT remains restricted to selected patients who are generally without advanced cardiac amyloidosis.

Beta-blockers and digitalis, commonly used for the treatment of congestive heart failure, are inefficient or appear to be dangerous in patients with AL and must not be used. Amiodarone should be considered as first-line therapy for arrhythmia.

Loop diuretics, given at high dosage in patients with severe fluid retention, are the mainstay of management. Patients should be instructed to control water intake, body weight and urine output on a daily basis in order to prevent overloads and subsequent cardiac insufficiency.

Anticoagulation therapy is mandatory in most AL amyloidosis.

Pacemaker implantation may be indicated in patients who develop symptoms of bradycardia or conduction disorders. A heart transplant should be considered in selected young patients with advanced amyloid cardiomyopathy, free from other co morbidities.

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Authors disclosure statement

The authors have no conflicts of interest.

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