# SYNDROMIC AND METABOLIC CARDIOMYOPATHIES

## Definition

Syndromic and metabolic cardiomyopathies present in the context of several syndromes or are due to inborn errors of metabolism. They may present with a restrictive pattern (Chapter 40), but this is variable, particularly as the disease progresses. An overview is provided in Table 1.

## Cardiac Amyloidosis

Amyloidosis comprises a group of diseases triggered by the misfolding of a soluble precursor protein. A total of 42 soluble precursor amyloidogenic proteins that can form extracellular amyloid fibrils have been identified to date.[1] Amyloidosis can be systemic or localized. Systemic amyloidosis can be hereditary (ie familial amyloidosis caused by genetic mutations inherited in an autosomal dominant manner) or acquired. The two most common forms, ***immunoglobulin light chains (AL) amyloidosis*** and the more prevalent ***wild-type transthyretin (ATTRwt) amyloidosis***, are acquired.[1]

Cardiac amyloidosis, a disease of myocardial infiltration by light chain or transthyretin fibrils, is the most common cause in the western world, and apart from diastolic may also cause systolic ventricular abnormalities.[2-4] Cardiac involvement is more common in ***primary amyloidosis***, which is caused by the production of immunoglobulin light chains (AL) by plasma cells, often in the context of multiple myeloma.[5 6, 7] Restrictive cardiomyopathy results from replacement of normal myocardial contractile elements by infiltrative interstitial deposits that begins in the subendocardium, and extends in the myocardium. Survival is poor in the presence of cardiac involvement and heart failure symptoms, being less than one year after diagnosis. ***Secondary amyloidosis*** is caused by the deposition of a non-immunoglobulin protein (AA) and can be ***transthyretin-related***, or due to a ***chronic inflammatory process.***[8, 9] Different mechanisms may be responsible for impaired contractility in cardiac amyloidosis, with an amyloid burden effect in transthyretin, but an idiosyncratic effect in light chain amyloidosis.[10] ***Hereditary transthyretin-related amyloidosis (ATTRm)*** is associated with >120 different mutations in the TTR gene that present variously from the third decade of life onward with permutations of peripheral and autonomic neuropathy, and sometimes involvement of other organ systems. One particular *TTR* gene variant, V122I, usually found in blacks, is associated with increased susceptibility to the development of late-onset predominant cardiac amyloidosis that closely mimics wildtype transthyretin cardiomyopathy. It is autosomal dominant, but sporadic mutations may also occur thus making a negative family history not a useful screening method. [11-13] ATTR*m* without the *TTR* V122I mutation has a better prognosis.[13] In general, the prognosis of patients who are diagnosed with ATTR-CM can be determined on the basis of National Amyloidosis Centre (NAC)

ATTR Stage, which is calculated at the time of diagnosis according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and estimated glomerular filtration rate (eGFR).[14]

***Wilde type transthyretin-related amyloidosis (ATTRwt)*** also called senile systemic amyloidosis, affects men over the age of 70 years, is caused by the aggregation of normal transthyretin (TTR) and predominantly results in cardiomyopathy. is probably due to age-related transthyretin misaggregation (no mutation present).[15, 16] Amyloid deposits derived from plasma transthyretin are present in the hearts of up to 25% of elderly people, and the associated clinical syndrome, predominantly comprising older men with restrictive cardiomyopathy that is often preceded by or associated with carpal tunnel syndrome, lumbar canal stenosis, and tendinopathy is more frequent than previously thought.[13 17] Co-existence of AS, as well as stroke volume index and global longitudinal strain are predictors of increased mortality.[18] Bilateral carpal tunnel syndrome is a common extracardiac manifestation of amyloidosis and usually predates overt cardiac amyloidosis.[19]

***Isolated atrial amyloidosis*** is also a form of senile amyloidosis and predisposes to AF.[20] Atrial biopsy revealed amyloid deposits in 7% of patients undergoing AF ablation, identifying early-stage cardiac amyloidosis.[21] Amyloid infiltration of the heart is common in the elderly and is typically subendocardial. The clinical spectrum of ATTR amyloidosis, in general, is heterogeneous and differs from the classic phenotype. Women are affected in a significant proportion, impaired LVEF is not rare, and only a minority have low QRS voltages.[22] Transthyretin cardiac amyloidosis is prevalent in up to 16 % of elderly patients with severe calcific AS.[23] Development of cardiomyopathy is less common with secondary amyloidosis and the prognosis is much better. Approximately 5% of patients diagnosed with hypertrophic cardiomyopathy have hereditary amyloidosis. Symmetric LV hypertrophy, thickened valves, and moderately depressed LV function in males >65 years old suggest ATTR rather than HCM.[24] However, asymmetric LV hypertrophy is the most common pattern in ATTR amyloidosis, unlike AL amyloidosis.[25] Staging systems for risk stratification have been described.[14, 16]

**Diagnosis**

AL amyloidosis should be included in the differential diagnosis for patients being evaluated for a variety of syndromes, particularly patients with nephrotic-range proteinuria, unexplained nonischemic cardiomyopathy, peripheral neuropathy, unexplained hepatomegaly, or atypical multiple myeloma.[1] CMR can help in the diagnosis of cardiac amyloidosis but cannot distinguish between AL and ATTR amyloid.[26] The diagnostic procedure is presented in Table 2 and Figures 1-4.

**Prognosis**

***AL amyloidosis*** has a poor prognosis, particularly in the presence of a monoclonal light chain in serum or urine, multiple myeloma, and hepatic involvement. Untreated patients with AL amyloidosis have a median survival of less than 6 months after the onset of heart failure.[27] Median survival is less than 50% in two years despite therapy with melphalan, steroids, immunomodulating agents (lenalidomide, and/or bortezomib), and autologous stem cell transplantation.[27, 28] Use of bortezomib,

dexamethasone, and an alkylating agent (BDex+AA) in patients presenting with symptomatic heart failure due to AL amyloidosis has been reported to improve survival.[29] The prognosis is better in light chain amyloidosis if it is recognized early and treated.[1] Bradyarrhythmias herald terminal cardiac decompensation in most patients with severe cardiac AL amyloidosis and prophylactic pacemaker insertion may be considered.[30]

Median survival in untreated patients with ***transthyretin-related amyloidosis*** reported to be 2.5 years after diagnosis for ATTR*m* caused by the *TTR* Val122I mutation, 6 years after ATTR*m* without the *TTR* Val122I mutation, and 3-5 years for ATTR*wt*.[13, 14, 16] ATTR*wt* (senile) systemic amyloidosis has a better prognosis,[6] but patients with decreased LVEF, and increased relative wall thickness have a limited survival of only 35.7% at 5 years.[15] However, the prognosis of patients with ATTR*m* the short- and mid-term prognosis of patients diagnosed with NAC Stage Ia and a loop diuretic equivalent dose requirement of <0.75 mg/kg, is good.[31]

**Therapy**

In AL amyloidosis, possibly because of an associated autonomic neuropathy, *ACEIs and ARBs* are rarely tolerated and may provoke profound hypotension even when prescribed in small doses.[32] *Digoxin* is potentially arrhythmogenic, particularly in amyloidosis. *Calcium antagonists* and *digoxin* bind to amyloid fibrils and can predispose to exaggerated hypotensive responses and toxicity despite normal serum digoxin levels, respectively.[33]. *Mineralocorticoid receptor antagonists* are associated with a reduced risk of mortality in patients transthyretin cardiac amyloidosis, and low-dose ***beta-blockers*** in patients with a LVEF ≤40%.[34] GLT2 inhibitors are also advised.[32] *AF* cardioversion in amyloidosis should be performed under cover of ventricular or transthoracic pacing with patches

Targets for disease-modifying therapies include TTR silencing, TTR stabilization, and TTR disruption. TTR stabilizers (***tafamidis, acoramidis,* and *diflunisal***) bind to the TTR tetramer and prevent misfolding and thus deposition of amyloid fibrils. TTR silencers (***patisiran* and *vutrisiran***) target TTR hepatic synthesis. TTR disruptors target the clearance of amyloid fibrils from tissues (under investigation).[3] Tafamidis, a benzoxazole derivative that binds to the thyroxine-binding sites of transthyretin and inhibits the dissociation of tetramers into monomers, represents the most effective therapy. In patients with heart failure due to transthyretin amyloid cardiomyopathy, it has been shown to reduce mortality and cardiovascular-related hospitalizations (30% compared to 43% with placebo over 30 months).[35] Initial experience with acoramidis is also promising.[36, 37] Patisiran, an intravenously administered RNA interference therapeutic that inhibits transthyretin synthesis, has resulted in decreased mean left ventricular wall thickness, global longitudinal strain, and NT-proBNP, in patients with hereditary transthyretin-mediated amyloidosis.[38] Vutrisiran, a subcutaneously administered RNA interference agent has led to a lower risk of death from any cause and cardiovascular events than placebo and preserved functional capacity and quality of life in patients with transthyretin amyloidosis with cardiomyopathy (HELIOS B RCT).[39] Cardiovascular magnetic resonance and extracellular volume mapping can measure amyloid burden in vivo, and can

track changes in cardiac amyloid burden and treatment response in transthyretin amyloid cardiomyopathy.[40]

Monoclinal antibodies and other agents are also being studied.[1, 3] Coramitug, a humanized monoclonal antibody targeting misfolded transthyretin is under study. Initial results are promising.[41] CRISPR-enabled in vivo gene editing for transthyretin amyloidosis is a new exciting possibility.[42] Recommendations are provided in Tables 3 and 4 and Figures 4 and 5.

## Cardiac Sarcoidosis

Cardiac sarcoidosis results from epithelioid cell granulomas infiltrating the myocardium and predisposing to conduction disturbances, ventricular tachyarrhythmias, and heart failure. It affects the basal septum, atrioventricular node and His bundle, focal regions in the ventricular free walls, and the papillary muscles.[43-46] Two-dimensional echocardiographic characteristics of cardiac sarcoid vary according to disease activity, and include wall thickening (>13 mm) due to granulomatous expansion and wall thinning (<7 mm) due to fibrosis. With scar retraction, aneurysms may develop, especially if the patient has been treated with corticosteroids. Cardiac involvement is clinically apparent in only 5% of patients with systemic sarcoidosis, but on autopsy the prevalence of cardiac disease of approximately 25%. In a study in Finland, the incidence of cardiac sarcoidosis was 5.3 cases per million.[47] The average age reported in cardiac sarcoidosis cohorts is 50–55 years, and women have a higher prevalence in the Japanese population, whereas a male predominance is reported in Europe and USA.[46]

**Diagnosis**

The main manifestations of cardiac sarcoidosis are conduction abnormalities, ventricular arrhythmias, and heart failure. [44, 48, 49] The diagnosis of cardiac sarcoidosis usually requires surrogate cardiac imaging biomarkers, and extracardiac histology of sarcoidosis.[44] Definite diagnosis requires endomyocardial biopsy which, however, has relatively low yield.[50] Cardiac sarcoidosis is the second leading cause of death among affected patients, after pulmonary sarcoidosis.[43]

Diagnostic criteria are presented in Table 5.

**Therapy**

Prednisone (30-80 md od) tapered over 6 months is used for **cardiac sarcoidosis**. Additional immunosuppression with methotrexate, mycophenolatemofetil, cyclosporine or infliximabe is recommended in non-responders to steroids,[48] raising the possibility that steroids might precipate electrical instability.[51] VT and electric storm frequently occur in the first 12 months after initiation of corticosteroid therapy.[52] Recent outcome data indicate 90% to 96% 5-year survival in manifest cardiac sarcoidosis.[44, 53] Patients with low LVEF, with high BNP levels, with VT/fibrillation history, and requiring ablation to treat VT are at high risk.[54]

Patients presenting with clinically manifest CS have a 10% risk of SCD over 5 years of

follow-up.[55] Thus, most patients require an ICD, and 25% of them need permanent pacing (Table 8 and Figures 5 and 6). Prognosis has improved but still when the condition presents with heart failure, the 10-year transplantation-free survival is only 53%. [47]

Recommendations are provided in Tables 6 and 7 and Figures 5-8.

## Iron overload cardiomyopathies

Iron overload cardiomyopathies are due to increased gastrointestinal (GI) iron absorption (hemochromatosis), or excess administration of exogenous iron by dietary sources or red blood cell (RBC) transfusions (hemosiderosis). They have either a restrictive or dilated phenotype that usually develops at later stages of the disease.[56, 57] The incidence of iron overload cardiomyopathy is increasing worldwide. Chronic blood transfusion is the main treatment for hereditary anemias such as thalassemia and sickle cell disease, that although prevalent in the Mediterranean basin, are also seen in other parts of the western world due to immigration. Causes of iron overload cardiomyopathy are presented in Table 3. Hereditary hemochromatosis is an autosomal disorder in which mutations of specific cause increased GI absorption of iron. Chronic transfusion is mandatory for the anemias listed. A unit of packed RBCs consists of 200 to 250 mg of elemental iron that accumulates in the body because there is no active excretion of iron.

Cardiac iron is regulated through transferrin-mediated uptake mechanisms. During iron overload transferrin is saturated, and nontransferrin-bound iron is released into the circulation and enters cardiac myocytes in the ferrous form through L-type calcium channels. Iron is then bound to ferritin and transported to lysosomes for degradation and long-term storage in the cardiac myocyte. When the antioxidant capacity of the cell is exceeded, iron is catalyzed by the rapid Fenton reaction producing hydroxyl ions, which is an extremely reactive free radical species that causes cell damage and death. Pathologic iron deposition begins initially within the epicardium and extends to the myocardium and then the endocardium, which helps explain the preservation of systolic function until very late in the disease. Thus, iron deposition is a problem of probably reversible storage than infiltration.[56, 58]

A restrictive pattern with LV diastolic dysfunction is usually seen, and the condition may later progress to dilated cardiomyopathy, although both forms may be independently seen. Iron accumulation occurs initially the ventricular and then the conduction system and the atrial myocardium, thus creating both conduction disorders and tachyarrhthmias due to inhomogeneity of conduction and refractoriness. Right heart failure can also be present early in the course of disease and be independent of left heart failure.

**Diagnosis**

Iron overload is considered when plasma transferrin saturation is>45-55% and serum ferritin >200

ng/ml in women or 300 ng/ml in men. [56] [59, 60] [33]

CMR is the only noninvasive method with the potential to assess quantitatively myocardial iron load by using techniques such as multiecho T2* gradient–echo sequences.[61] The time constant of decay for GE-induced relaxation time is known as T2*. The following stratification scheme has been proposed:[62]

- T2* >20 ms indicates low risk for the imminent development of congestive heart failure.
- T2*= 10-20 ms indicates intermediate risk of cardiac failure.

T2* <10 ms indicates high-risk that needs intensification of chelation therapy

**Therapy**

Iron overload cardiomyopathies are dealt with phlebotomy that removes 400 to 500 ml of blood (200 to 250 mg of iron) at each session, thus mobilizing iron from the organs where it is stored for the production of hemoglobin. Early in the disease, this procedure is done up to 1 or 2 times a week to obtain a target ferritin below 20 ng/ml and then maintenance phlebotomy is performed 2 to 4 times a year.[63] Routine monitoring of hemoglobin, ferritin, and hematocrit is essential during maintenance phlebotomy. Chelation therapy is used in patients not suitable for required phlebotomy such as those with significant anemia or malignancy. It removes iron by binding to it and then excreting the compound in urine and bile. Presently available chelators include deferoxamine (subcutaneous or IV) and oral deferiprone.[56, 64] Dietary interventions to minimize or eliminate iron ingestion are not feasible or useful. New therapeutic modalities being studied are erythrocytapheresis, novel chelating agents, calcium channel blockers, hepcidin induction (a gene regulating iron homeostasis in the body), gene therapy in beta thalassemia or sickle cell disease (genetically modulating autologous stem cells implanted by a vector into the target cell), and donor-matched healthy stem cell transplantation.

## Muscular dystrophies

Patients with myotonic dystrophy (type 1-Steinert's disease or type 2) due to mutations in dystrophia myotonica protein kinase ***(DMPK)*** gene have also a high risk of developing cardiac disorders such as cardiomyopathy and heart failure, conduction defects, and arrhythmias, both late and, especially, within the first years of diagnosis.[65, 66] The ***dystrophin*** gene (***DMD***) is responsible for Duchenne and Becker muscular dystrophy, and X-linked dilated cardiomyopathy that develops in young men with rapid progression from heart failure to death, due to ventricular tachycardia or ventricular failure.[66, 67] The primary presenting symptom in most dystrophinopathies is skeletal muscle weakness, and these patients are identified by raised amounts of the muscle isoform of serum creatine kinase. Polymorphisms in genes encoding ***HLA-D antigens***,[68] and a single nucleotide polymorphism on chromosome 6p21,[69] have also been related to DCM susceptibility. ***Mitochondrial diseases*** are a group of disorders caused by defects in the mitochondrial respiratory chain that impair oxidative phosphorylation. Therefore, organ systems that rely on aerobic metabolism are primarily affected.

When skeletal muscle is involved, alone or in conjunction with other organ systems, the term mitochondrial myopathy is used. Respiratory gas profiles indicative of severe and premature lactic acidaemia can be the only diagnostic clue.[70] Although once considered rare, these disorders are being increasingly recognized with a prevalence of up to 13.1 per 100 000 births based on some studies.[71]

Patients with muscular dystrophies should be closely followed for consideration of the need of pacing or ICD (Table 9, and Figure 10).[66] Prophylactic treatment with *ACE inhibitors* has been associated with a significantly higher overall survival and lower rates of hospitalization for HF in patients with Duchenne muscular dystrophy.[72]

## Glycogen storage disorders

Glycogen storage disorders, including Anderson-Fabry disease, Pompe disease, Danon disease (lysosome-associated membrane protein 2 [LAMP2]), and protein kinase AMP-activated noncatalytic subunit gamma 2 (PRKAG2)-deficient cardiomyopathy, are systemic diseases associated with variable degrees of cardiac involvement.[2] The ECG and echocardiographic features are similar to those seen in hypertrophic cardiomyopathy. ***Anderson-Fabry's disease,*** the most common glycogen storage disorder, is an X-linked autosomal recessive disease that results from the progressive accumulation of glycosphingolipids due to lysosomal alpha-galactosidase A deficiency.[73] Affected patients have microvascular disease of the kidneys, heart, and brain. Cardiac involvement is not manifested until the third or fourth decade of life and may mimic hypertrophic cardiomyopathy (Table 8 and Figure 9).

Replacement of alpha-galactosidase A by chaperone molecules such as oral migalastat reduces wall thickness in Fabry disease.[74]

## Mitochondrial Cardiomyopathies

Mitochondrial cardiomyopathies are a heterogeneous group caused by dysfunction of mitochondrial energy production due to genetic mutations affecting mitochondrial or nuclear DNA. They include a wide range of cardiac manifestations and are frequently associated with other multisystemic symptoms, including skeletal myopathy, neurological deficits, and metabolic disturbances. Specific examples of mitochondrial cardiomyopathies due to mtDNA disorders are ***MELAS/MERF syndromes***, whereas examples of nuclear gene defects are ***Barth syndrome***, ***Leigh syndrome***, ***Friedreich's ataxia***, ans ***mitochondrial inorganic pyrophosphatase deficiency***.[75]

Advances in genetic testing have improved diagnostic accuracy, but early identification remains challenging due to the variable clinical presentation and clinical overlap with other cardiomyopathies.

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