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Amyloid cardiomyopathy – the true burden, current approach to diagnosis and treatment (RCD code III-3A.1, III-3A.2)

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Amyloid cardiomyopathy (CA) was previously considered to be a rare disease, however, it is currently more frequently diagnosed owing to the application of rapidly developing imaging modalities. The deposition of misfolded, insoluble proteins in the extracellular matrix of various tissues and organs plays a key role in the pathogenesis of systemic amyloidosis. Until now, there have been over 30 different precursor proteins described which have the potential to form amyloid fibrils. However, two types account for over 95% of CA cases: immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) [1, 2]. Amyloid accumulation in the heart not only profoundly impacts the function of cardiomyocytes, but importantly, it also affects the extracellular space of the myocardium. Thus, in the course of CA, a progressive diastolic dysfunction is typically observed, while in more advanced stages, systolic dysfunction is seen as well, resulting in a hypertrophic or restrictive cardiomyopathy phenotype [3, 4, 5]. AL is characterised by an underlying plasma cell clone which produces structurally abnormal monoclonal free light chains (FLC) [6]. Median survival of untreated patients with cardiac involvement is less than 6 months [7]. Misfolding of transthyretin (prealbumin, TTR), a transport protein for thyroxine and retinol, is the source of 2 distinct forms of ATTR: acquired wild-type ATTR (ATTRwt), also known as senile amyloidosis, and hereditary ATTR (ATTRm). Importantly, the prevalence of ATTR may be higher in specific patient subpopulations, reaching 13% in heart failure with preserved left ventricular ejection fraction (HFpEF), 5% in hypertrophic cardiomyopathy (HCM), and 16% in severe aortic stenosis [8, 9, 10].

In a review article published in the *Journal of Rare Cardiovascular Diseases,* Ioannis Boutsikos et al. evaluate the current approach to diagnosis and treatment of CA [11]. The authors provide important insight into the epidemiology, pathology, and clinical presentation of the disease. Currently available imaging modalities are presented, including echocardiography, cardiac magnetic resonance, and nuclear medicine techniques. Additionally, the article presents possible treatment options for patients with AL and ATTR.

Importantly, in all cases of CA there are general considerations regarding the management of cardiovascular complications, including different approaches to classic heart failure (HF) therapy. Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers may lead to hypotension in these patients [12]. Moreover, digoxin and non-dihydropyridine calcium channel blockers should be avoided, as they bind irreversibly to amyloid fibrils and can cause severe side effects [13]. A combination of loop diuretics and mineralocorticoid receptor antagonists has been shown to be safe. Depending on the clinical stage, AL therapy may include: melphalan, dexamethasone, bortezomib, autologous haematopoietic stem cell transplantation, as well as new generation proteasome inhibitors, bendamustine, and monoclonal antibodies [14].

On the other hand, novel emerging ATTR therapies are currently under investigation and there are numerous particles being developed. Gene therapy includes patisiran, a short interfering RNA (siRNA) molecule, and inotersen, an antisense oligonucleotide. Both drugs were investigated in patients with neuropathic ATTRm variants, however, the efficacy and safety of the drugs in CA has yet to be verified [15, 16, 17, 18]. Inotersen has been shown to increase the risk of adverse effects including glomerulonephritis (3%) and life-threatening thrombocytopaenia (3%). Furthermore, tetramer-stabilizing therapy is becoming available. Recently, the ATTR-ACT trial, which included patients with the cardiac form of ATTR, reported a reduction in mortality and urgent hospitalisation rates in the group treated with tafamidis [19]. Another drug, diflunisal, reduces the progression of neurological symptoms in patients

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with ATTR, however, potential adverse effects remain an important concern [20]. Moreover, a phase 2 trial confirmed the safety and efficacy of another particle (AG10) in patients with ATTR CA, and a phase 3 trial is currently in progress [21]. The combined therapy of doxycycline and tauroursodeoxycholic acid (TUDCA) may also affect amyloid degradation [22, 23].

It is crucial to emphasise that aside from the classical approach to CA diagnosis based on histopathology, a new non-invasive diagnostic algorithm has been recently established. Single-photon emission computed tomography (SPECT) with bone-avid tracers (3,3-disphono-1,2-propanodicarboxylic acid (DPD), methylenediphosphonicacid (MDP), and pyrophosphate (PYP)) has become an important technique for identifying ATTR patients. Positive SPECT, defined as Perugini marker uptake of grade 2 or 3, without concomitant detectable monoclonal protein in the serum or in the urine, justifies ATTR diagnosis [24, 25, 26]. Histopathological examination of cardiac tissue and amyloid typing remain an available diagnostic approach for those patients who do not meet the above diagnostic criteria.

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