Epidemiology

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Abbreviations and Acronyms

CAD	Coronary artery disease
DCM	Dilated cardiomyopathy
ECG	Electrocardiography
EMB	Endomyocardial biopsy
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
ICD	Implantable cardioverter device
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
NGS	Next-generation sequencing
SCN5A	Sodium channel protein type 5 subunit alpha
WGS	Whole-genome sequencing

Dilated cardiomyopathy (DCM) is a cardiac disease characterized by LV dilatation and impaired systolic function. An acquired dilated phenotype may result from a variety of factors including coronary artery disease (CAD), hypertension, myocarditis, valvular and congenital heart disease, drug toxicity, alcohol abuse and metabolic disease. Indeed, the diagnosis of "primary" DCM is often of exclusion. Among the forms of primitive DCM, familiar forms and idiopathic forms are identified [1–4].

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G. Sinagra et al. (eds.), *Dilated Cardiomyopathy*,
https://doi.org/10.1007/978-3-030-13864-6_2

Table 2.1 Major epidemiologic studies in dilated cardiomyopathy

Study	Incidence/prevalence
Torp et al. 1978	3/100,000/year [20]
Bagger et al. 1984	0.73/100,000/year [21]
Williams et al. 1985	8.3/100,000 [22]
Codd et al. 1989	36.5/100,000 [6]
Dolara et al. 1989	1.8/100,000/year [23]
Rakar et al. 1997	6.95/100,000/year [5]

The epidemiology of this condition is quite complex, due to misdiagnosis, continuous reclassification and changing definitions. Furthermore, since investigations were performed on small populations in specific geographic areas and were not representative of the general population, epidemiological studies on DCM are affected by many limitations. Another, but substantial, limitation of epidemiological studies conducted on this pathology depends upon the lack of standardized diagnostic criteria [5].

Initial estimations of prevalence data for DCM came from a population-based study by Codd et al. conducted on the Olmsted Country population (Minnesota, USA) between 1975 and 1984. According to this study, the prevalence rates were higher for men, with a male/female ratio of 3:1 [6]. Age- and sex-adjusted prevalence rates reached 36.5/100,000 subjects, and incidence rates were found 6/100,000 person years. Younger patients (<55 years) were more frequently affected (incidence up to 17.9/100,000). Data related to the epidemiology in different ethnicities suggest a 2.7-fold increased risk associated with black race [7]. Death certificates from the National Center for Health Statistics' confirmed a 2.5-fold increased risk in blacks more than in whites, with black men having the highest prevalence (27/100,000 in black men versus 11/100,000 in white men) [8]. In Italy, the first data on the incidence of DCM go back to a prospective post-mortem study on consecutive necropsies performed during a 2-year period (November 1987–November 1989) in the Department of Pathology at Trieste University. Incidence of DCM at autopsy was estimated at 4.5/100,000/year, while clinical incidence in the same period was 2.45/100,000/year. The total incidence was 6.95/100,000/year in accordance with the study by Codd et al. [5, 6]. Table 2.1 shows a summary of major epidemiologic studies.

2.1 Towards Contemporary Clinical Epidemiology in Dilated Cardiomyopathy

The 2008 position statement from the European Working Group on Myocardial and Pericardial Diseases was a definitive turning point and shed new light upon the dark side of cardiomyopathies [9]. Cardiomyopathies were defined as "myocardial disorders in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality" [10].

They were grouped into specific morphological and functional phenotypes and further divided into familial and nonfamilial forms. Diagnostic criteria have two main objectives: to support and facilitate the recognition of the disease and to allow the early diagnosis in affected asymptomatic family members. The consensus paper combined a clinical mind-set with first- and second-level diagnostic tools (i.e. ECG and echocardiography), placing the emphasis on family history of cardiac and neuromuscular diseases. The diagnostic paradigm shifted from a pathophysiological mechanism to a morphological and functional point of view, and the new awareness of a familial pattern in this disease built the basis of relatives screening [11].

In recent years, the diagnosis of DCM became reliable even in centres of different countries, thus allowing multicentre studies with more numerous and representative populations of well-studied patients. Furthermore, female sex gained attention in scientific literature and gender differences became an important topic to address.

Diagnostic criteria only partially overcame the difficulties faced in epidemiologic studies because of the challenging diagnosis and clinical presentation of the disease. Hershberger and colleagues estimated DCM prevalence on the basis of the known DCM to HCM ratio of ≈2:1. Therefore the surrogate DCM was found to be about 1–250 subjects [12], resulting from the early diagnosis, more effective treatments and a reduced mortality of patient partially linked to the identification of DCM in asymptomatic subjects. Current guidelines report a prevalence of familial DCM ranging from ≈30 to 50% of cases, with 40% having an identifiable genetic cause [13–15].

Table 2.2 shows the frequency of DCM in special categories.

DCM was originally considered a rare disease, and the possibility of a familiar substrate was ignored. Over time, DCM was found to be a major cause of HF affecting especially young patients, with absent or nonsignificant comorbidity and a long life expectancy, thus emerging as a major indication to heart transplantation [1]. The need to improve diagnostic accuracy for this population gave new life to scientific literature. DCM started to be considered a systemic condition rather than an isolated disease, and ventricular dilatation was found a common pathway of several cardiac diseases [3].

The studies carried out more recently were not built upon the solely basis of the phenotype, thus reflecting the epidemiology of the disease with higher accuracy. However, despite major efforts, the true incidence and prevalence of DCM still remains to be determined.

Table 2.2 Frequency of dilated cardiomyopathy in special groups

Categories	Prevalence ratios
Female to male	Between 1:1.3 and 1:1.5 [7, 23]
White (W) to African-Americans (AA)	1:2.45 W 11/100,000 AA 27/100,000 [7]
Familial forms	30–50% [14]

2.2 Genetics and Future Perspectives

As previously discussed, it has been known for decades that familial clinical screening in idiopathic DCM would reveal a significant amount of first-degree affected subjects (20–48%). However, only in the last few years, the role of genetics has become predominant in the approach of DCM patients, and the complexity of genetic mechanisms, genotype and environment interactions and genotype-phenotype correlations have become clearer. A fundamental role for these achievements has been played in recent years by the technological progress with the so-called next-generation sequencing (NGS) techniques, also used to sequence the entire human genome (coding and noncoding regions of DNA), referred to as whole-genome sequencing (WGS), with panels of dozens of genes at reduced cost [16].

In the most recent reports, approximately 40% of DCM cases have an identifiable genetic pathogenic variant. An important issue in this setting is the vast genetic as well as phenotypic heterogeneity in familial DCM, meaning that more than one mutation could be found and sometimes different morphological forms are showed in a single family: this is a major obstacle in clinical practice and in genetic report interpretations, because unreported pathogenic mutations must be validated, a process that needs time and delays the screening of other family members [17].

Thanks to the efforts in this field, a growing number of genes involved in DCM have been identified, and currently most panels cover 30–40 genes. Recently, many European centres have put their data together to create the first "Atlas of the clinical genetics of human Dilated Cardiomyopathy" [18].

Nowadays, the role of genetics is becoming more and more important in clinical practice. In fact, there is an increasing evidence that identifying a disease-causing variant may have important patient management implications in terms of severity of the disease, prognosis and survival rates. For example, McNair et al. reported that 1.7% of DCM families have SCN5A gene mutations linked to a strong arrhythmic pattern [19] and that Lamin A/C mutation carriers have a well-known risk of major ventricular arrhythmias/sudden death and conduction system abnormalities: this evidence may lead clinical cardiologist to consider ICD implantations in a cluster of patients that do not match the usual criteria indicated by the HF guidelines [20].

Epidemiology of DCM is rapidly changing. Furthermore, genetic testing may identify asymptomatic carriers, which lead to redefine prevention strategies, sport recommendations and ICD implantation. Nevertheless, it may guide reproductive decision-making, which could further modify the incidence and prevalence of DCM in the future decades [21].

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