Familial Cardiomyopathy: A Clinical, Before the Bench Diagnosis

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The recent clinical and genetic advancements in establishing the genetic basis of inherited cardiomyopathies are introducing a novel medical need that extends the cardiologic care from the proband/index patients to their families [1]. Family screening studies of consecutive series of patients diagnosed with Dilated Cardiomyopathy (DCM) (that was considered for more than 20 years the paradigm of post-viral disease) have shown that more than 50% of the so called “idiopathic” DCM are familial. This implies that several members of the same family are either affected or will develop the disease later on in the course of their life [2-8]. A simple family history or, even better, the clinical screening of relatives (using routine tools as ECG and echocardiography) can identify either affected, asymptomatic family members or individuals showing echocardiographic or electrocardiographic abnormalities that could predict the development of the disease. Re-screening/follow-up of family members provides the evidence that, in variable intervals of time from the first clinical evaluation [available studies include ranges from 3 to 10 years], 6-10% of relatives develop the disease according to WHO criteria [5-8]. The evidence that other types of cardiomyopathies are familial and have a genetic origin extends to Hypertrophic Cardiomyopathy (HCM), Arrhythmogenic Right Ventricular Cardiomyopathy [ARVC] and Restrictive Cardiomyopathy [RCM]. HCM has more than 70% of familial cases, ARVC has at least 50% of familial cases and RCM, which includes a broad spectrum of diseases involving the heart only, or the heart and the skeletal muscle, or one of the phenotypes of more complex and systemic diseases [1,9-11].

The position statement on cardiomyopathies of the ESC acknowledges familial cardiomyopathies and supports family screening studies

The recent position statement of the WG on Myocardial and Pericardial Diseases of the European Society of Cardiology formally introduced the concept of “familial” and “non-familial” cardiomyopathy thus providing the indication for the diagnosis of familial cardiomyopathy and the rationale for performing clinical family screening by using routine, non-invasive cardiologic tools and clinical genetics [1]. Family screening and monitoring documented that most cardiomyopathies have a genetic origin, and these data will further generate, in a near future, clinically relevant information on the natural history of the cardiomyopathies, including their pre-clinical and pre-symptomatic phases [2-6].

Knowledge on the natural history of cardiomyopathies will highlight the criteria for diagnosing “early cardiomyopathy” which is an uncovered need in cardiology. Although the concept of any type of “early” cardiomyopathy is apparently easy to perceive, diagnostic criteria are still not coded and early diagnosis could dramatically modify the future management of cardiomyopathies.

Genetic testing now provides genetic diagnosis

The parallel progression of molecular genetics and availability of molecular tools for gene screening facilitated the investigation of candidate genes in single large families in small selected series and in progressively larger groups of patients sharing the major cardiac phenotypes [HCM, DCM, RCM and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)] [11-12].

The number of known disease-genes is extremely high [up to 35 in familial DCM, 12 in HCM, 8 in ARVC/D and several others in RCM] and, paradoxically, defects of same genes may cause different phenotypes and vice versa, different genes may cause similar phenotypes (i.e. LMNA gene) [11-12]. The fact that different genes cause similar diseases [genetic heterogeneity] does not mean that the diseases are identical, but simply that more diseases sharing the major phenotype (dilated and dysfunctioning heart, hypertrophic heart, restrictive heart, etc.) can be grouped under a same clinical class or group of diseases.
Extending the concept from the single disease-gene to the pathway in which the given gene plays its role, the genetic heterogeneity can be considered in a broader fashion. For example, desmosome functional and structural pathway and ARVC/D [12], or sarcomere functional and structural pathway and HCM [11]. Therefore, although several genes may cause HCM, sarcomere genes will cause sarcomeric HCM, while non-sarcomeric HCM can be caused by a variety of different genes such as those involved in lysosome function (typically Anderson Fabry Disease, a non-sarcomeric “HCM”) or in other storage diseases such as Danon Disease, or HCM with WPW [13-18]. The key problem in planning genetic testing is the clinical characterisation of the HCM phenotypes that are caused by defects of sarcomeric genes versus those that are caused by defects of genes playing in non-sarcomeric pathways. This simple and intuitive concept offers diagnostic advantages, for example by restricting the number of genes that should be analysed in the different cardiomyopathies.

The genetic and allelic heterogeneity are limiting the translation of molecular genetics to the existing large clinical series diagnosed with DCM, HCM, RCM and ARVC/D. The overall number of affected individuals expected in Europe on the basis of available prevalence data is extremely high considering the known prevalence values available in the current literature (1:500 HCM, 1:2.500 DCM, 1:500 ARVC, and very rare for RCM) [10,16-18]. By joining existing information, both published or orally presented, the current translational benefits of genetic testing and screening seem to be limited to no more than 1% of affected individuals in Europe. The limited translational process is negatively impacting the diagnostic application of molecular genetics, active in very few centres in Europe, restricting the potential benefits that include preclinical, presymptomatic and prenatal diagnosis, early treatments and clinical trials, lifestyle guidance and support.

The genetic heterogeneity and the high number of disease genes indicate that genetic testing should be clinically guided and addressed to the analysis of specific disease genes.

A cardiomyopathy-oriented mindset based on available knowledge, biotechnology tools and clinical genetic evidences should be adopted once clinical markers associated with the main phenotypes have been proven to recur in subgroups of cardiomyopathies caused by defects of a same gene or of a group of genes playing in the same pathway and having similar functional effects.

Strategies that can make the molecular genetic work-up selectively oriented through a candidate or a few candidate genes rather than to the entire set of disease-genes are based on characterisation of the clinical phenotype. The clinical approach that could facilitate further translation from the major phenotype (for example, all DCM) to the specific subgroups (for example, DCM caused by defects of LMNA gene) is the search for clinical markers associated with the common phenotype. These markers constitute red flags capable, if appropriately framed in the context of the major phenotypes, to raise specific clinical hypotheses. Typically they can be cardiologic markers (such as conduction disturbances), morphological features (such as left ventricular non compaction), extra cardiac (such as hearing loss or myopathy) or biochemical markers (such as variations of the ion levels, serum CPKemia, or lactacidemia) [19-27].

The contribution of clinical genetics in a family whose members underwent clinical screening can be equally contributory: the pattern of inheritance may, by itself, contribute to restrict the spectrum of hypotheses. Easy examples are X-linked or matrilineal or recessive diseases versus the more common autosomal dominant pattern of inheritance that recurs in the vast majority of inherited cardiomyopathies. Therefore a DCM inherited as X-linked recessive trait excludes LMNA as a candidate gene in a male patient with DCM and conduction disease. Vice versa, a father-to-son transmission excludes dystrophin gene defects. Analogously, a matrilineal inheritance substantially excludes the majority of candidate genes (autosomes), especially when heterogeneous phenotypes, both cardiac and extra cardiac, can be recognised in the proband initially presenting with symmetrical hypertrophy that later evolved through dilatation and dysfunction, as well as in the family members that may show myopathy or encephalopathy.

If additional clinical traits (both cardiac, such as electrocardiographically detectable signs - conduction disturbances, PR interval, WPW, QRS voltages, both supraventricular and ventricular arrhythmias - or extracardiac traits such as hearing loss, palpebral ptosis, juvenile cataract, myopathy, encephalomyopathy, mental retardation), are clinically investigated and identified in either probands or relatives, the request of genetic testing is clinically oriented and more likely to provide positive and useful results. Obviously the above contributors cannot be usefully employed if cardiologists are not aware of the current knowledge in this setting and if simple instruments such as Mendelian and matrilineal laws are not used.

**Genetic diagnosis is a promising contributor for the future disease-specific management of cardiomyopathies**

The management of cardiomyopathies is based on their phenotype, symptoms and complications (typically chronic heart failure, arrhythmias and tromboembolic events). The identification of the genetic causes of cardiomyopathies is providing the basis for a novel disease-specific diagnostic approach with impact on risk stratification [21,28,29]. The availability of medical treatments, interventional procedures, mechanical support (new-generation VADs now close to being used as a permanent form of “destination” therapy), and heart transplantation, makes the correct risk stratification and timing of clinical decisions an integrated process in the management of these diseases [30]. The awareness of the risk of cardiomyopathies as a whole is roughly incorporated; into clinical practice the tailoring to individual risk is still far from optimal.

In HCM, the arrhythmogenic risk is currently stratified on the clinical ground [31]. Early data on genotype-phenotype correlations suggested that HCM caused by defects of MYH7 gene. Defects show higher risk of life-threatening arrhythmias than those caused by mutations of other disease genes. More recent data show that the arrhythmogenic risk can be high also in HCM caused by defects of MYBPC3 gene. The still undetermined prevalence of double or compound heterozygosity (up to 8%) and the existence of still unknown disease genes raise the suspicion that part of the discrepancies existing in geno-phenotype correlations is due to incomplete genetic testing results or interpretation. Although currently available guidelines do not include genotyping for risk stratification, an increasing number of patients are being genotyped in Europe and the request is progressively increasing. Existing criteria and indications for risk stratification are still debated and the consensus on ICD implantation timing is not unanimous.
Most cardiologists stratify the risk on a case by case basis and frequently encounter the dilemma as to whether a LV wall thickness few millimetres less than the 30mm (which is one of the criteria for ICD implantation) discriminates on a relevant clinical decision in the absence of other criteria. The risk of evolution of HCM through dilatation and end-stage heart failure (about 10% of all HCM) is unpredictable on currently available data. Patients carrying double or compound heterozygosities seem to be more exposed to this risk. This type of evolution is also observed in non-sarcomeric HCM such as those associated with mutations of the LAMP or PRKAG2 gene.

In DCM, the prognostic stratification relies on the criteria established for heart failure; recent advances in genetics of DCM documents that the overall group of idiopathic DCM is constituted of several diseases caused by different genes, with different phenotypic and prognostic profiles. The most consistent data are those available on DCMs associated with defects of the LMNA gene, which are characterised by high risk of sudden death. The risk recurs in both early and late phases of the disease and seems to be intrinsically related to the molecular defects and related functional and structural effects [21,28,29]. This concept implies that the risk may be present in patients in NYHA class I as well as NYHA class IV. Therefore the molecular diagnosis of DCM caused by LMNA defects should enter the clinical work-up of these patients, as the disease displays very high clinical malignancy and should be protected by early ICD implantation, regardless the criteria proposed by current guidelines.

In RCM the genetic advances of the molecular basis are mostly addressed to desminopathies (typical phenotype is RCM plus conduction disease) and troponinopathies (RCM without conduction disease). The relevant prognostic information for the former is the involvement of skeletal and smooth muscle, which could contribute to dysphagia and dyspnoea independently from (and additionally to) the myocardial disease; once transplanted, patients with skeletal and smooth muscle involvement should not receive statins, which worsen the myopathy. Vice versa, troponinopathies display a high arrhythmogenic risk, which may recur in the absence of significant hypertrophy [10].

Finally, the genetics of ARVC/D is now a matter of investigation in large clinical series and the most frequent disease genes (the desmosome genes) play their role in the same pathway of intercellular junctions, both function and structure. The prognostic stratification does not rely on genetics but the increasing number of genotyped cases will soon provide the evidence of a future role of genetic testing in prognostic stratification [32].

CONCLUSION

Modern cardiology is assisting in a revolutionary approach to the diagnosis of heritable cardiomyopathies. The study of the clinical phenotypes that has been largely abandoned in the last decades is now the key element for making molecular genetics the powerful tool for translation of research products from bench to bedside. Cardiologists should implement their clinical investigative capability and their attention should extend from probands to relatives; criteria for early diagnosis should be formulated to promote the novel culture of preventive cardiology for cardiomyopathies.

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REFERENCES


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