Hypertrophic cardiomyopathy: the pathological features and the molecular pathogenesis

Hipertrofik kardiyomiyopati: patolojik özellikler ve moleküler patogenez

Dear Editor,

I have read the article "Hypertrophic cardiomyopathy: pathological features and molecular pathogenesis – Review" published in the December 2004 issue (1) of the Anatolian Journal of Cardiology. I would like both to criticize the peer-review system and the peer-reviewed article.

Nowadays, I observe an easiness of writing a review for authors and interpretation of the paper for reviewers. Initially, the Anatolian Journal of Cardiology is pertaining to the world cardiology journals as it is indexed in Index Medicus and PubMed. In a way, it is the responsibility, honour, and credit of all Turkish cardiologists. To be "cited" and having a high "impact factor" is needed to became exclusive in the arena of cardiology journals. We should make all efforts as a "whole" for our journal, The Anatolian Journal of Cardiology, as a mission. Therefore, the responsibility belongs not only to the authors but also to the reviewers. The reader will expect to find the recent comprehensive and compact knowledge while reading the papers. In my opinion, the mission and responsibility of authors are as follows:

- The author should clearly put to the preparation of data strategy on paper (like writing the methodology of original paper). For instance, type of database system, eg PubMed, Index Medicus and the years for scanning. The author should avoid merely the convey of information of classic textbook information. The recent "state of the art papers" should be cited and future direction of the topics should be discussed as well.
- The duty and mission of reviewers is not simply to fulfill a decision of acceptation/ rejection process. In case of acceptance, they should convey the review paper to better, ameliorate, and built up further. Each sentence and comment should be filtered cautiously, attentively, and meticulously. The reviewer should realize the importance of putting a paper into cardiology arena.
- The editor of the journal should select and invite the specialists in the topic. The merit, qualification, and competence are indispensable when they decide to add important review paper in the journal. For many investigators, the collection of data for their original article is feasible only from state of the art peer review papers.

Secondly, I would like to criticize briefly the aforementioned review paper (1). If we put into practice the report of the prevalence of hypertrophic cardiomyopathy (HCM) in USA and Europe (1/500), approximately 150,000 subjects suffer from HCM in Turkey. The HCM is the most common genetic cardiovascular disease, and sudden cardiac death (SCD) has been its most threatening and devastating consequence. The most important cause of SCD are malignant ventricular arrhythmias. Such events usually occur in previously healthy individuals without significant symptoms or as the initial clinical manifestation of the disease. Interestingly, I have not found a word of "arrhythmia". Besides, the identification of high-risk patients and efforts at prevention of sudden death represent important clinical target in HCM. However, it has become clear that the link between genotype and the risk of SCD is not simple. From a practical perspective, given the above limitation and the absence of widespread availability of genetic testing for HCM, genotype assessment does not form part of the current risk factor stratification of patients with HCM. The aim of treatment of HCM is the prevention of the SCD. Although the positive predictive value is low, however, since the negative predictive values of risk factors is high, screening the patient in respect of presence of risk factors is very important. Finally, some recent state of the art papers should be put into account in the topic of HCM while writing a review of HCM (2-4).

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Author's Reply

Dear Editor,

"Hypertrophic cardiomyopathy (HCM) is one of the most common genetic disorders of the cardiovascular system. It is a heterogeneous disease both clinically, morphologically and genetically. Genetic heterogeneity of HCM is beyond the variety of the disease genes, further describing various mutations in these genes. The mutation detected in many cases is the one which has not been previously known and which is specific for that family. This genetic feature necessitates the detection of mutation technically and limits genetic researches only to the research centers.

The potential advantage of genetic heterogeneity in HCM is due to making genotype-phenotype correlations. The shared phenotype in HCM patients is hypertrophy, which particularly influences the interventricular septum. The degree, distribution, initial age, type of hypertrophy and the severity of clinical symptoms vary greatly. Detection of the previous genetic disorder gives the opportunity to recognize phenotype related to specific genotypes.

The most sensitive and specific method for clinical diagnosis of HCM is echocardiography. The echocardiographic diagnosis is made by detecting cardiac hypertrophy in cases who do not have any other reason for hypertrophy. However, usually hypertrophy does not occur until puberty. If the penetrance is also low, detection of hypertrophy, and so diagnosis of the disease is not possible until middle ages. The same difficulty is encountered in patients who have other reasons for hypertrophy and in elderly people. Detection of hypertrophy echocardiographically is insufficient in these patients. The accurate diagnosis is made by displaying the mutation genetically. In families who carry low- penetrance mutation, although many individuals are genotypically altered, they do not display a disorder echocardiographically. It was thought that since hypertrophy develops late, with the traditional clinical screening methods which were used before molecular studies, diagnosis in children and young adults would be difficult. This interval for diagnosing hypertrophy has prolonged to middle ages since the detection of myosin binding protein C (MYBPC) mutations. Adults with no phenotypic expression but whose genotypes are positive, are rarely encountered. Mutations in sarcomeric protein genes except MYBPC are silent until adolescence, and occur in early adulthood with significant clinical features. MYBPC, on the other hand, is usually asymptomatic until middle ages and even in the elderly. In these adults, the frequency of HCM phenotype and the time when it will develop is not clear. These results show that diagnosis of HCM can be made in the elderly as well. Typical symptoms seen in elderly HCM patients such as dyspnea, angina and syncope mix with other diseases (hypertension, valvular diseases, coronary artery disease and etc.). The typical symptoms of elderly HCM patients are similar to those seen in young people. However some morphologic features, different from the ones seen in young people such as septum curve, distortion of the left ventricular outflow may be encountered. Because of this, patients with the risk of developing HCM should be in follow up regimens during adulthood. Since late onset of disease may be due to a hereditary gene defect, relatives of the patient must also be examined.

Detection of mutations responsible for HCM will allow routine investigation of mutations and preclinical diagnosis of asymptomatic patients. This is particularly important in children, because in children with positive genotype and negative phenotype there is a probability for development of left ventricular hypertrophy (LVH) as the body is complementing its development. Also it will be possible to make risk detection by genotype-phenotype correlation. It is very important to determine a genetic marker for sudden cardiac death (SCD) encountered in HCM patients. SCD usually occurs as an initial symptom of the disease. Clinical and morphological factors used to determine people under the risk of SCD vary widely. Most clinical symptoms seen in patients with HCM do not help diagnosing some serious complications such as SCD. The risk of SCD is independent of both the degree and distribution of LVH. Genetic findings have shown that different mutations in a gene may correlate with this risk and that they may be useful in the detection of risk.

The study by Maron et al about the prevalence of HCM is based on detection of phenotype echocardiographically, it does not take into consideration the genotype frequency of the patients. Since the clinical features of the disease range from asymptomatic to SCD, the prevalence rate of 0.2% detected in this study may become higher in another study regarding genotype. By detecting mutation genetically the frequency of the disease will be more realistic, thus providing earlier preventions.

Since HCM is a multifactorial and poligenic disease because of varieties in both the initial age and the severity of the disease even in the same family and personal differences of people who evaluate echocardiography, and environmental and modified other genes which probably play role in the pathogenesis, diagnosis of the disease causes many conflicts. Since more than 20% of adults with mutation are clinically normal, results which will be obtained from DNA mutation analysis will lighten the insufficiencies of clinical screening programs." (1)

The information mentioned above is quoted from the thesis study of Çam FS. (1). As can be understood from the text there are some conflicts regarding the prevalence of the disease, children or adults who carry pathological mutations in the molecular level but cannot be diagnosed clinically, do carry the disease in the community. Also there are not accurate data of the prevalence of the disease in Turkey. Ser260Cys, Ala423Val, Val605Met, Leu714Pro, Asp778Glu mutations in β-myosin heavy chain (MYH7) gene, g21452insTT mutation in MYBPC gene and Val→ter mutation in 27. exon are new mutations (except Asp778Glu mutation) which have been detected in Turkish people for the first time in studies complementing the thesis study (unpublished data).

Continuing studies in Turkish community comprising more patients and gene locations will both lighten the prevalence of the disease and will help to determine the treatment and prognosis of patients by making phenotype-genotype correlations. The subject of this writing is limited to pathological features and molecular pathology of the disease and does not include clinical features, treatment of the disease and SCD. As can be understood from the quotation, the importance of SCD for this disease is obvious.

The criticism on duties of the editor and referees are appropriate and realistic since it is very important that experienced and authorized referees correct the writing they examine, thus supporting young scientists for writing more qualified and scientifically sufficient papers. Of course it should be preferred that reviews are state of the art papers, and that they should be written by experienced, important authors. However, if opportunities are not given to young scientists, no "experienced and important scientist" will be left after the experienced scientists leave the world. Then how will this insufficiency of the specialized areas be compensated?

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