A clinical and Molecular Genetic Study on Egyptian Children with Hypertrophic Cardiomyopathy

THESIS

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Abstract

Hypertrophic cardiomyopathy (HCM) is a primary genetic disease of the myocardium characterized by hypertrophy of left ventricle and interventricular septum and inherited in an autosomal dominant fashion. It is one of the leading causes of sudden cardiac death especially in the young. This study included 10 patients with isolated HCM and 10 normal children as a control group. The aim of the work is to determine whether exon 13 in MYH7 gene is a site for mutations among Egyptian children in the studied sample. Detailed History, clinical examination, echocardiography were done to all patients. Molecular screening for mutations in exons 13 & 14 of MYH7 gene was done to the patients' & control groups. Screening results revealed; normal amino acids sequence in exon 13 among studied sample, normal polymorphism detected among both patients' & control groups. Conclusion: Mutations in exons 13 & 14 of MYH7 may not be the cause of HCM among studied sample.

Key words:

- Hypertrophic Cardiomyopathy.
- Egyptian children.
- MYH7 gene.
- Exon 13 & 14 mutations.

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List of Abbreviations

- ACE: angiotensin converting enzyme
- AD: autosomal dominant
- AHA: American heart association
- AR: autosomal recessive
- ARVC: arrhythmogenic right ventricular cardiomyopathy
- ASH: asymmetrical septal hypertrophy
- AV: atrioventricular
- BP: blood pressure
- BSA: body surface area
- CPB: cardiopulmonary bypass
- CUCH: Cairo University Children's Hospital
- DCM: dilated cardiomyopathy
- DM: diabetes mellitus
- DNA: deoxyribo nucleic acid
- HCM: hypertrophic cardiomyopathy
- HOCM: hypertrophic obstructive cardiomyopathy
- HR: heart rate
- ICD: intracardiac defibrillator
- IHSS: idiopathic hypertrophic subaortic stenosis
- IVS: interventricular septum
- LV: left ventricle
- LVEDD: left ventricular end diastolic dimension
- LVEF: left ventricular ejection fraction
- LVH: left ventricular hypertrophy
- LVOTO: left ventricular outflow tract obstruction

- M: month
- MRI: magnetic resonance imaging
- MyBPC: myosin binding protein c
- MYBPC3: myosin binding protein c gene
- MYH7: myosin heavy chain gene
- PG: pressure gradient
- PPI: permanent pacemaker implantation
- PWT: posterior wall thickness
- RCM: restrictive cardiomyopathy
- RVOTO: right ventricular outflow tract obstruction
- SAM: systolic anterior motion
- SCD: sudden cardiac death
- SD: standard deviation
- TDI: tissue Doppler imaging
- WHO: World Health Organization
- Y: year
- Z score: is the SD for echocardiographic measurements in relation to age & BSA
- ACTC1: alpha cardiac actin gene
- B-MyHC: beta myosin heavy chain protein

Introduction

Introduction

Hypertrophic cardiomyopathy (HCM) (OMIM #192600) is a primary cardiac disease of the myocardium of autosomal dominant inheritance. It is characterized by left ventricular hypertrophy without chamber dilatation, in the absence of either a systemic or other cardiac disease, which may cause a similar magnitude of hypertrophy (Wang et al., 2010).

It is a genetic disease that results mainly from mutations in genes encoding proteins of the Sarcomere, the most common of which is MYH7 gene that accommodates for about 25 % of HCM mutations (Alcalai et al., 2008).

HCM is a complex and confusing disorder that has been a subject of intense scrutiny for the past 50 years and of great interest to cardiologists, genetists and pathologists. And that is attributed to its diverse pathological, clinical and molecular heterogeneity (Maron et al., 2003).

The estimated prevalence of HCM in the general population is 1:500. It equally affects males and females. Moreover, it is increasingly detected in many races and countries (Maron et al., 1995).

HCM has got variable clinical presentations; from completely asymptomatic to severe symptoms (arrhythmias, angina, syncope…etc.) & even death. It is considered as one of the leading causes of sudden cardiac death (SCD) of young apparently healthy individuals (including athletes) (Maron et al., 2009).

It can present at any age and may be detected in infancy, during childhood and adolescence, or as an accidental finding in the elderly, consequently the pathologist may be the first to encounter a case of HCM at autopsy (Hughes, 2004).

The pathological hallmark of the disease is myocyte hypertrophy and disarray (Shirani et al., 2000).

It can be divided into 2 types; non obstructive HCM or hypertrophic obstructive cardiomyopathy (HOCM) (Davies and McKenna, 1994).

Echocardiography is the cornerstone in diagnosis of HCM (Losi et al., 2010), which is clinically diagnosed by the presence of primary cardiac hypertrophy and a preserved or enhanced LVEF (Maron, 2002).

Predictive genetic testing has an important role in early identification of asymptomatic relatives of HCM patients in attempt to decrease the risk of SCD (Christiaans et al., 2008).

Variable management strategies are being implied according to patients' manifestations; pharmacological therapy (as β-blockers & Ca channel blockers) & non-pharmacological therapy as transcatheter septal ablation or surgical myomectomy of the hypertrophied septum. The later is considered as the "gold standard" for therapy of HOCM with an excellent functional outcome (Marian, 2009).

Aim of the Work

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Clinical assessment of cases with hypertrophic cardiomyopathy to detect familial cases.

Molecular screening for exon 13 of MYH7 gene to define whether it is the most common mutational hot spot among studied HCM cases or not.

Providing genetic counseling concerning nature, inheritance, recurrence risk and implications of the disease to cases proved to have a documented mutation.