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Original Article

Clinical manifestation and outcomes of children with hypertrophic cardiomyopathy in Kosovo

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ABSTRACT

Background and objectives. Identification of the manifestations, assessment and follow up of children with hypertrophic cardiomyopathy (HCM) by transthoracic echocardiography may be important for clinical management and our understanding of pathogenesis.

Methods. We present a comprehensive analysis of 43 children seen in Kosovo, 23 were male, aged between 4 months and 9 years at first presentation (median of 2 years and 3 months).

Results. Cardiac failure, seen in almost half of them, was the most common presenting feature. At admission, the chest x-ray revealed an increased cardiothoracic ratio, to a mean of 72% in 6 infants and to 65% in 37 older children. Measured by transthoracic echocardiography, 28 children had asymmetric hypertrophy of left ventricle while 15 had concentric hypertrophy. Left ventricular ejection fraction was depressed in 21 children. Patients with cardiac failure received various combinations of diuretics, B-blockers, ACE inhibitors and anticoagulant therapy (aspirin). Death occurred in 8 children, in 4 of them shortly after admission, the other 4 left Kosovo and continued examination and treatment abroad Kosovo; their death has been confirmed by family members. The remaining 32 were followed- up for a mean 42 months, with a range from 5 to 115 months. Surgical intervention was not performed to any of them, despite the clinical and echocardiography indications due to a limitation of resources. Recovery was noted in 14 children but still requiring anti-heart failure medications. Slightly over two-fifths died. Of those with asymmetric form, 45% died, half of those presenting in infancy, and 89% of those who presented at admission with signs of cardiac failure.

Conclusion. The results of our study show that similar to many centers, the etiology of HCM is often uncertain. In the absence of etiology, treatment aimed at the cause is either impossible or, at best, empirical.

Key words: hypertrophic cardiomyopathy, left ventricular hypertrophy, heart failure, myectomy transthoracic echocardiography.

Hypertrophic cardiomyopathy (HCM) is defined as the presence of hypertrophied, non-dilated ventricle in the absence of a hemodynamic disturbance that is capable of producing the existent magnitude of wall thickening (e.g., hypertension, aortic valve stenosis, hyperthyroidism, catecholamine secreting tumors, etc.).[1] It is the most common inherited cardiovascular disease, with diverse etiology, affecting populations worldwide and the leading cause of sudden cardiac death in young people. While sarcomeric gene defect has been reported to be the primary cause of HCM in adults, in children the disease is seen in a wide variety of multisystem and cardio specific disorders. It is common to group these diseases as familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders).[1,2] HCM in childhood is a heterogeneous disease with variable progression. The disease has been reported from several centers and countries, and described for several groups. Incidentally,

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Table I. Summary of some publications on childhood hypertrophic cardiomyopathy.

Leadauthor	Year	Country	Etiology	N° of patients
Heinrich K	1995	Germany, USA	mixed	600
CecchiFs	1995	Italy	mixed	202 (134 >older 15 years)
Alan W. N	1996	Australia	mixed	80
Sanae Mi	1998	Japan	mixed	309
Barry J. Maron	2000	USA, Italy	mixed	744
Steven D. Colan	2007	USA	mixed	855
Cristina Basso	2009	Italy, USA	mixed	115
JoseOliva-Sandoval	2010	Spain	mixed	152
Georgios K Efthim	2010	Greece	mixed	380

most of the reports have drawn attention to the generally severe course of the disease, especially to its unsatisfactory response to standard anti-heart failure therapy (Table I).[3] Reports have mostly come from tertiary centers, raising the possibility of a selection bias in favor of very sick children. Unfortunately, reports from Balkan countries on the disease are still scanty.

The aim of this article is to present a diagnostic approach, treatment and outcome of children with HCM in Kosovo, as a small country with limited technical and human resources, and to compare our findings with recent publications in this field. The objective of this study was to provide an account of children with HCM as seen in the country of Kosovo, diagnosed by echocardiography and analyzing the data of 43 patients, registered at the Unit of Cardiology, from January 2007 to December 2017, aged from 21 days (3 weeks) to 9 years.

Material and Methods

Pediatric Clinic in Prishtina, part of the University Clinical Center of Kosovo in Prishtina, Kosovo, provides pediatric cardiology services, of secondary and tertiary level. Practically, all children with known or suspected cardiac disease are referred to our institution from the regional hospitals for cardiac evaluation and care. This system has enabled us to build a database and provide services to virtually all patients with pediatric cardiac disease in Kosovo. This project is part of data relating to HCM that forms the material for this study, which aimed to provide an account of the disease as seen in Kosovo. The study protocol was approved by the Medical Ethics Committee of the University Clinical Center of Kosovo in Prishtina (1098/26.07.2018). Written informed consent was obtained from all patients.

The field of the research

We commenced our study in January 2007, where summaries of patients with cardiac disease were recorded in the database of the cardiology department. Two pediatric cardiologists in the Department of Cardiology evaluated cardiological examinations, where 43 children fulfilled the standard criteria for the diagnosis of HCM, and they present the subjects of this study. Prior to the examination, weight and stature were recorded and the body surface area was calculated by the Dubois and Dubois formula. None of the patients were receiving cardiovascular medication at the time of admission. The evaluation of each child comprised a short familiar and personal history, physical examination, chest radiography, electrocardiogram, and trans thoracic echocardiography. Determination of levels of the cardiac enzymes in serum was not considered a critical investigation. Echocardiography evaluation was performed in all patients, at presentation and during follow-up visits by the same two pediatric cardiologists. Follow-up investigations, comprising mostly of electrocardiograms and trans thoracic

echocardiographs, were performed as often as the clinical state warranted. The results obtained are shown in absolute and relative numbers.

Results

Both sexes were affected, with a non-significant predomination of males, there being 23 males (53%) and 20 females (47%). At initial presentation, all patients were aged between 3 weeks and 9 years, the median age being 13 months and mean 22.33 months. Of this number, 8 children(18%) were less than 12 months old, 23 children (53%) aged between one and 5 years, and 12 (28%) were more than 5 years old. To half of them, the reason for cardiac examination was a systolic heart murmur. At admission, the chest x-ray revealed an increased cardiothoracic ratio, to a mean of 72% in 6 infants and to 65% in 38 older children. All of the patients were Kosovar Albanians and citizens of Kosovo.

Twelve children in our study manifested echocardiography signs of LVOT, half of them with asymmetric HCM. Using continual and color Doppler imaging technique, in 11 children at the level of OTLV the pressure gradient (PG) was registered, measuring from 3.2m/s (PG = 41mmHg) to 5.3m/s (PG =112 mmHg).

Of our overall group, 4 children died shortly after admission, and 4 children died while being treated abroad, with signs of arrhythmia or sudden death, despite therapy coverage. Five of them were with positive family history of cardiomyopathy.

The children who died in Kosovo were 3 males and 1 female, the youngest child died at age 26 months, the other at age 32 months, 3yaers and 4 months and 6 years and 2 months (Table II) . Four 4 children died while being treated abroad, with signs of arrhythmia or sudden death, despite therapy coverage. Five of them were with positive family history of cardiomyopathy.

Etiology

In 18 children (41%), siblings had reportedly suffered from the same disease, and these patients were categorized as being familial. Four of them (three males and one female) were cousins, 16 members of this family were suffering from HCM. Eight of them died during this period (one child and six adults),

Table II. Age at diagnosis, standard and antiarrhythmic drugs and age at death of children with HCM at our study.

Initials of children	Age at diagnosis	Standard medical therapy	Antiarrhythmic therapy	Age at death
B.L. (male)	19 months	Kaptopril/Enalapirl Furosemide, Aspirin Spironolactone	Flecainide (start) Amiodarone (continue)	32 months
B. A (female)	11 months	Enalapirl, Furosemide, Aspirin Spironolactone	Sotalol (start) Felcainide (continue)	26 months
A.S (male)	8 months	Kaptopril Furosemide, Aspirin Spironolactone	Atenolol (start) + Amiodarone	3 years 4 months
S.D. (male)	33 months	Enalapirl, Furosemide, Aspirin Spironolactone	Sotalol (start) + Amiodarone	6 years 2 months
R.D. (male)	4 years 5 months	Enalapirl, Furosemide	Flecainide	Left Kosovo
I.R. (male)	6 years	Kaptopril Furosemide, Aspirin	Amiodarone (start) Propafenone (continue)	Left Kosovo
T. R. (female)	5 years 6 months	Kaptopril Furosemide	Sotalol	Left Kosovo
O. B. (female)	3 years 8 months	Enalapirl, Furosemide	Propafenone (start) Amiodarone (continue)	Left Kosovo

and all had sudden death. Four children (9%) had LEOPARD syndrome disease, but without pulmonary hypertension. In the remaining patients, etiology of HCM was unknown.

Clinical state at presentation

At presentation, we found evidence of congestive heart failure in 4 children, in 12 children an atypical heart murmur was noted during the routine examination, while, the remaining 27 were referred for cardiac examination following radiographic findings and disturbances in cardiothoracic ratio. The cardiothoracic ratio in this group of children ranged from 44 to 76% with a mean of 58%. In 26 other children, in whom the ratio could accurately be evaluated, it ranged from 59 to 77, with a mean of 65%. In Fig. 1. we presented the echocardiography of the patient with hypertrophic cardiomyopathy.

Medication

All 4 children who presented with cardiac failure received various combinations of standard anti-heart failure drugs. Later in the course of the disease, 3 children received infusions of Amiodarone when they developed ventricular rhythm disturbances and became critically ill. Furosemide and Spironolactone

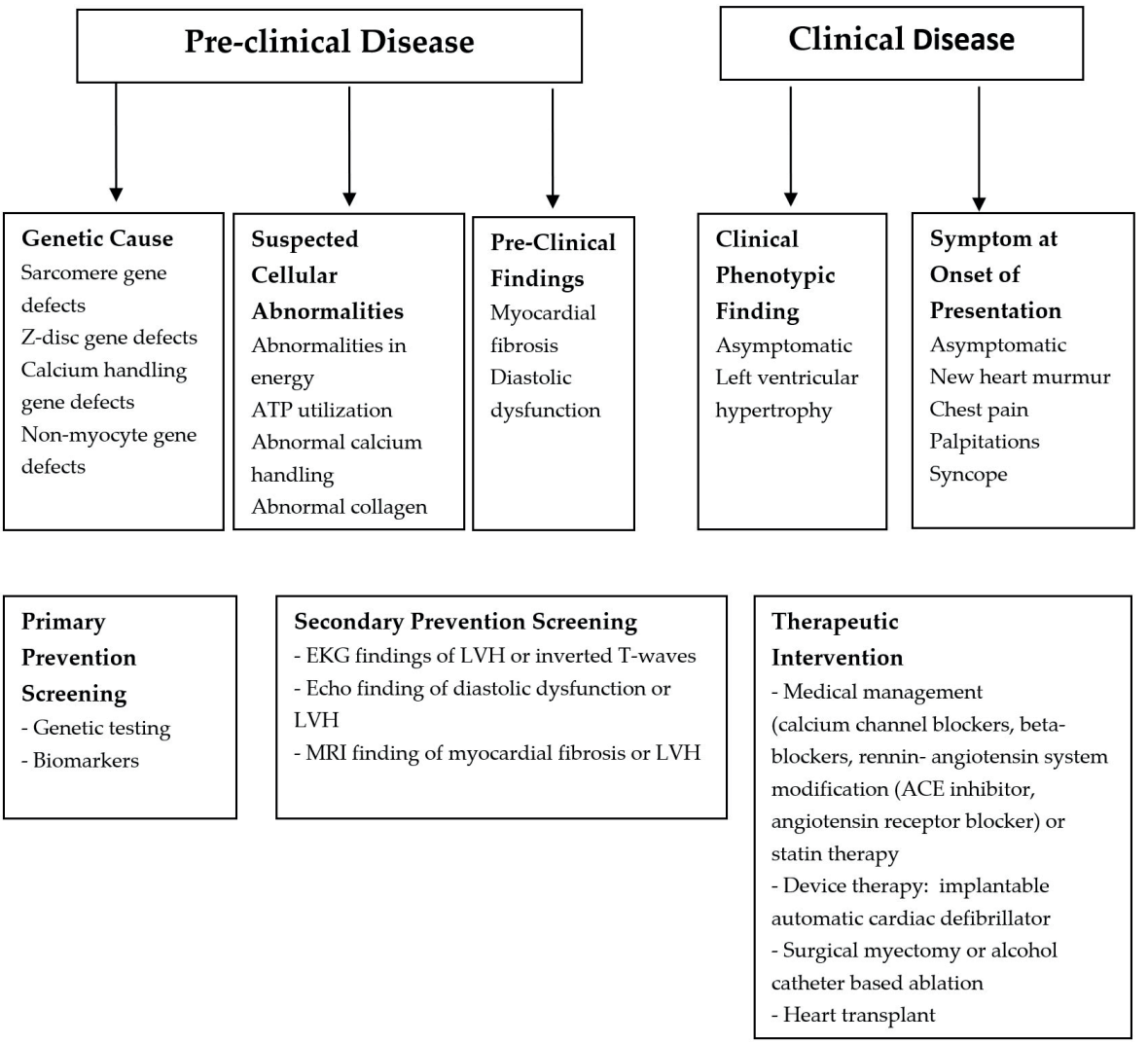

Fig. 1. Screening strategies for hypertrophic cardiomyopathy at each stage of disease.[10]

were standard part of the therapy during the whole time of hospitalization. Twenty-eight children, including 4 children with signs of cardiac failure, received Captopril and 8 of them developed a Captopril-induced intolerable cough, which necessitated the drug replacement by Enalapril. Initially, all patients were treated with a ß-blockers (Propranolol, Atenolol or Sotalol), while Carvedilol was additionally administrated in 4 children, because intolerable hypotension developed. Standard oral antiarrhythmic therapy was based on the using one of oral antiarrhythmic medication (Propafenone, Flecainide, Sotalol or Amiodarone). In 28 patients we instituted empirical treatment with Aspirin.

Discussion

Hypertrophic cardiomyopathy (HCM) is an important disease affecting populations worldwide. It is the most common inherited cardiovascular disorder and the leading cause of sudden death in young people. Several community-based epidemiologic studies have estimated the risk of sudden cardiac death in teenagers and young adults with HCM to be approximately 1% per year.[4] Associated risk factors for sudden cardiac death include: A family history of HCM related premature death, unexplained syncope, a hypotensive or attenuated blood pressure response to exercise, recurrent no sustained ventricular tachycardia and massive left ventricular hypertrophy (a wall thickness > 3 cm). The prevalence of HCM has been estimated to be at most 0.2% in the United States, affecting about 1 in every 500 adults. Based on the data of the high incidence of HCM and often cause of the sudden death some countries have applied screening for HCM as routine examination.[5]

The primary purpose of screening for HCM is to identify affected children before they experience sudden death. Early recognition of the disease, either in the pre-clinical stage (before left ventricular hypertrophy develops) or in the clinical stage (after left ventricular hypertrophy has developed) may allow for earlier treatment with the potential to alter disease progression. A secondary aim of screening would be to identify family members with either pre-clinical or clinical disease, thus offering them the same therapeutic benefits as offered to the index case. As a result of these phenotypic and age-related variations, any diagnostic or screening strategy for HCM must include a variety of components. These range from simple measures such as personal and family history, the physical examination, electrocardiography or trans thoracic echocardiography (Fig.2).[5,6] More

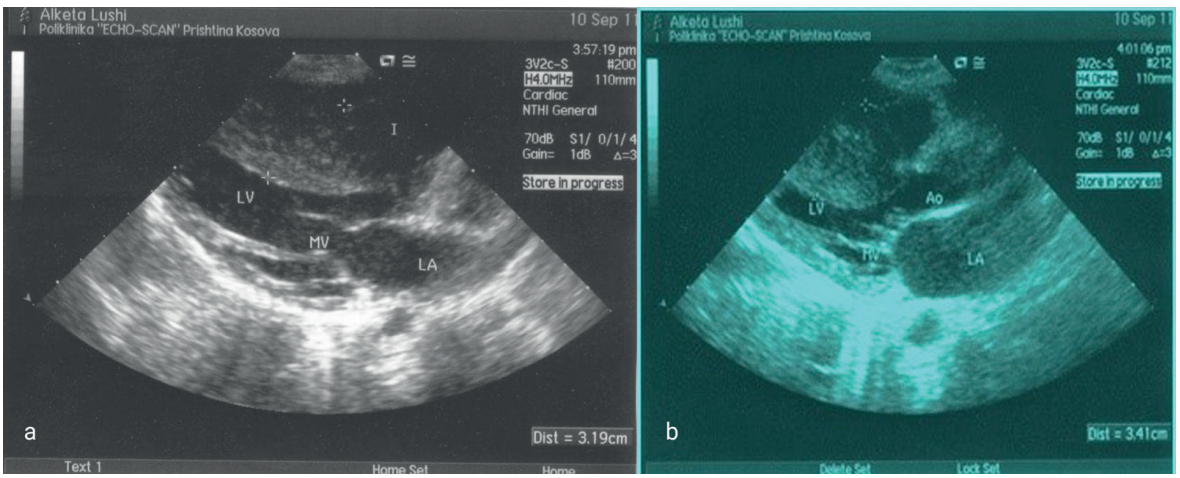

Fig. 2. Parasternal left ventricular long-axis echocardiografic section obtained a patient in diastole (a) and systole (b) with hypertrophic cardiomyopathy.

LV- left ventricle, LA- left atrium, Ao- Aorta, MV- mitral valve.

complex examinations such as cardiac magnetic resonance imaging, biomarkers, and genetic analyses may be appropriate for diagnosis and care in specific cases. The best application of these many modalities is yet to be determined, and will undoubtedly vary between locations, population and availability.[7] During a mean follow-up of 46 months, approximately one-fifth of the children died, others improved but continued to require anti-heart failure and anti-arrhythmic medications. Also, these figures raise the very important question on why the standard medical treatment of the disease is so frequently.

Management of symptoms

Hypertrophic cardiomyopathy is a complex disease with variation in presentation, symptoms, severity, and response to therapy. Medications are often prescribed to treat symptoms and prevent further complications. Medications such as beta-blockers and calcium channel blockers relax the heart muscle, allowing it to fill better and pump more effectively. Other medications may be prescribed as needed to control heart rate or decrease the occurrence of arrhythmias. The goals of the therapy in HCM are symptom control and prolongation of survival. Symptoms such as chest pain, dyspnea, and exercise intolerance can often be managed medically, and surgery has been successful in certain patient groups.[8] The clinical importance of outflow obstruction to the natural history of HCM and the associated symptoms has been highly controversial. The presence of outflow tract obstruction has not been found to be associated with an increased risk of sudden death; patients with outflow tract obstruction are at greater risk for symptoms and progression to death due to heart failure. Although the ability to define the etiology of HCM has improved over time, this goal still remains elusive.[9]

Despite the recent progress in treating children with HCM therapy based on the use of beta-blockers, diuretics, calcium channel blockers, antiarrhythmic drugs (Sotalol, Flecainide, Propafenone, Amiodarone), pacemaker therapy (asynchronous ventricular pacing), implantable cardioverter defibrillator (ICD), in extremely severe forms surgical myectomy and percutaneous radiofrequency septal reduction, survival rate is still low.[3] Our account of HCM, based on our experience at the National Referral Center in Prishtina corroborates the dismal accounts of the disease which have been published previously from other centers.

While many children with HCM are asymptomatic, some typical prognostic profiles are well recognized. One group of patients has symptoms of cardiac failure, including exertional dyspnea, orthopnea, chest pain, and general fatigue. This group of patients has normal or hyper contractile left ventricular function, with or without obstruction of the left ventricular outflow tract (LVOT). While significant obstruction typically causes symptoms, there are also asymptomatic patients who do not have obstructed outflow tract, and symptoms are due to factors such as diastolic dysfunction of the left ventricle, mitral regurgitation or micro vascular dysfunction.[10,11]

A second well recognized group is made up of the patients with atrial fibrillation and its complications, such as embolic stroke. The final group with a typical clinical profile is made up of those who are at risk of sudden cardiac death. Most children in our study with clinical manifestation of HCM belong to the first group (29 children), no child were registered in the second group, and 14 children were registered in the third group, all having family HCM.[12]

Most of the anatomical abnormalities in HCM can be assessed reliably by trans thoracic echocardiography. These include: Abnormal mitral valve motion, a reduction of the anteroposterior dimension of the left ventricular outflow tract and of the left and right ventricular cavities, increased thickness of the interventricular septum and the posterior left ventricular wall. Comparison of the hemodynamic and echocardiography data showed that some degree of abnormal

mitral valve motion during systole may occur in the absence of left ventricular outflow tract obstruction. Other, hitherto unrecognized, abnormalities in HCM detected by this technique are: Aortic valve regurgitation in 1/3 of children with evidence of left ventricular outflow tract obstruction at cardiac catheterization, left ventricular inflow tract obstruction at the mitral valve level associated with gross septal hypertrophy and abnormal forward displacement of the posterior mitral valve leaflet and of the chordae tendineae during systole.[5,6]

Hypertrophic obstructive cardiomyopathy is an uncommon cause of left ventricular outflow tract obstruction in children. In symptomatic patients, with a severe form of LVOT obstruction, open heart surgical myectomy has been the only therapeutic option. Recent data in treating patients with obstructive form of the HCM, using percutaneous radiofrequency septal reduction, as an alternative to surgical myectomy, from many centers showed enviable results, especially after having failed pharmacological therapy.[4,13] Transthoracic and transesophageal Doppler echocardiography is a gold standard to document the degree of myocardial septal hypertrophy and the gradient at rest across the left ventricular outflow tract. Twelve children from our study group developed severe form of obstructive cardiomyopathy and, due to technical limitation; none of the children were treated surgically or by using radiofrequency procedure.[14,15]

Cardiac magnetic resonance imaging (CMRI), is considered the gold standard for determining the physical properties of the left ventricular wall and can serve as an alternative screening tool when an echocardiogram provides inconclusive results, especially in the identification of segmental lateral ventricular hypertrophy where echocardiography cannot be accomplished alone.[16] A limitation of our study is the lack of CMRI application in examination and diagnosis of children with HCM as a result of the deficiency of MRI equipment at our institutional the time of study.

Currently, cardiac transplantation is the ultimate surgical resort for patients who do not respond to medical or surgical treatment. But the option is available only in relatively few centers, most of them in United States of America and in Europe. For the pediatric cardiologist who has no recourse to cardiac transplantation, caring for the child with HCM and treatment-resistant cardiac failure remains a very challenging assignment.[17] Quite often, the choice must be made between continuing treatment with barely effective conventional drugs, adding Carvedilol and Amiodarone, implantation of the implantable cardioverter defibrillator, despite their ill-defined pediatric dosing and lingering uncertainties about efficacy in children. In all probability, the choice will be influenced as much by the available resources as by the embraced philosophies of care.[17,18]

A limitation of our study relates to the diagnosis of pathohistological type of HCM which, for the technical reason, was completely based on the clinical and transthoracic thoracic echocardiography examination. Indeed, the recent statement of the American Heart Association on cardiomyopathies does not recommend endomyocardial biopsy as a test for the diagnosis of disease even though endomyocardial biopsy, evaluated using the Dallas criteria, remains the gold standard for diagnosis. Endomyocardial biopsy is not feasible in most centers that provide care for children with cardiac disease, including HCM.[19,20] The clinical implication of all these factors is that in many centers, including ours, the etiology of HCMis often uncertain. In the absence of etiology, treatment aimed at the cause is either impossible or, at best, empirical.

A limitation of our study with regard to the treatment was also the inability to apply pulse Holter monitoring for accurate diagnosis of the type of heart rhythm disturbances. Pathological findings with pulse Holter monitoring contribute to the prevention of sudden death or to determining the indication for implantation of the ICD. Despite the strong indication for this

treatment and sudden death of 7 members from the same family, none of the children from our study group was treated with the ICD.[21,22]

HCM is often severe in our patients. While the clinical diagnosis is usually easy, and the hemodynamic severity can be ascertained fairly accurately, the etiology is frequently uncertain. The response to standard anti-failure medical and surgical treatment is often unsatisfactory and cardiac transplantation is not feasible. For the time being, the hope for improved survival in our center, and similar centers, are hinged on on-going international efforts to manipulate multifactor mechanisms implicated in HCM.

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