CARDIOMYOPATHY

The diagnosis of hypertrophic cardiomyopathy

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Although the pathology of hypertrophic cardiomyopathy (HCM) was first described by French pathologists in the mid 19th century, it remained for the virtually simultaneous reports of Brock and Teare in England some 43 years ago to bring modern attention to this fascinating entity.[1][2] Subsequent to these surgical[1] and pathological[2] observations, there has been an almost exponential growth in the number of research reports and in our knowledge of HCM, and a number of extensive reviews have been published.[3–9] HCM was initially thought to be relatively rare, but it is now recognised to be an important cause of morbidity and mortality in people of all ages. In tertiary referral populations the annual mortality is 3–4% per annum (higher in the young) and 1–2% per annum in non-referred populations. It occurs in 1 in 500 live births, making it as common as cystic fibrosis, and is the most common cause of sudden death during athletic endeavour in young people. The diagnosis of HCM is therefore of great importance, particularly in the young where sudden death is such a risk.

More recently, the results of molecular genetic studies have resulted in a quantum leap in our basic knowledge and understanding of the Mendelian dominant inheritance of HCM and have far reaching prognostic and clinical implications. HCM is now described as a heterogeneous disease of the sarcomere in that more than 150 different mutations in 10 different sarcomeric proteins have been shown to cause HCM[8] (table 1). These molecular genetic studies are already having important clinical implications in that some mutations carry a benign prognosis, whereas others, possibly interacting with various growth factors, have increased penetrance, early onset of manifestations, and a bad prognosis, thus explaining the malignant family history noted in some instances. Because of the time consuming nature of these molecular genetic studies, they are only currently available

Table 1 *Genetics of hypertrophic cardiomyopathy (HCM)*

Mendelian dominance: variable penetrance
A disease of sarcomeric proteins
  α and β myosin heavy chain
  Troponin T and I
  α Tropomyosin
  Myosin binding protein C
  α Cardiac actin
  Myosin (essential and regulatory) light chain
  Titin

A genetically heterogeneous disease.
Mutations in the 10 listed sarcomeric proteins have been shown to account for the Mendelian dominant inheritance of HCM.

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Table 2 *Types of HCM and approximate incidence**

Types of HCM	Incidence (%)
Left ventricular involvement	
Asymmetrical hypertrophy	95
Ventricular septal hypertrophy	80
Apical hypertrophy	9
Midventricular hypertrophy	4
Rare types	2
Symmetrical (concentric) hypertrophy	5
Right ventricular involvement	–

*At the Toronto General Hospital where approximately 1300 patients are registered in the HCM clinic. The incidence of the different types of HCM varies considerably among different centres.

research centres. However, within five years it is expected techniques for genetic diagnosis will become more generally available and hence more generally applicable.

In addition to the genetically determined form of the disease, HCM may also occur in older patients (HCM in the elderly), where it is often related to hypertensive left ventricular hypertrophy and/or age related changes of the heart (sigmoid septum).[10] It is important to realise, however, that a certain percentage of cases of HCM in the elderly will be genetically determined in that certain mutations, such as those in myosin binding protein C, have delayed penetrance and late onset of disease (up to age 60 years).[11]

Just as the inheritance of HCM is heterogeneous, so are the phenotypic manifestations, even in a single family cohort, with the same molecular genetic defect. HCM may be defined as left and/or right ventricular hypertrophy of unknown cause that is usually, but not always, asymmetrical, and associated with microscopic evidence of myocardial fibre disarray. Ventricular septal hypertrophy is by far the most common type of asymmetrical hypertrophy, with apical, midventricular, and rarer types of asymmetrical hypertrophy being far less common (table 2). The extent of hypertrophy at any given site can vary greatly and bears importantly on the manifestations of the disease.[5]

From a clinical standpoint, it is very important to classify HCM haemodynamically (table 3). The subaortic obstruction is by far the most common form of obstructive HCM and may be latent (provocable), labile (variable), or there may be a persistent obstruction at rest (resting obstruction). Figure 1 demonstrates the pathophysiology of the subaortic obstruction and the concomitant mitral regurgitation, both of which are caused by systolic anterior motion of the anterior and/or posterior mitral leaflet.[7] The two forms of obstructive HCM may co-exist in the same patient. Non-obstructive HCM may be defined as a patient having no obstruction at rest or on provocation.

Clinical diagnosis

Family history

A detailed and accurate family history is of obvious importance in dealing with patients in whom HCM is a diagnostic possibility. In families in whom several family members have

Table 3 Haemodynamic classification of HCM

Obstructive HCM
  Subaortic obstruction
  Midventricular obstruction
Non-obstructive HCM
  Normal (supranormal) systolic function
  Impaired systolic function (end-stage HCM)

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See text for more detail

heart disease at a relatively young age, HCM is a distinct possibility. That possibility is increased significantly if there are sudden deaths at a young age in a family. Once the diagnosis is established in a member of a family, other family members should be screened with ECGs and echocardiograms in keeping with the known Mendelian dominant inheritance of the condition.

Symptoms

Patients with obstructive HCM typically complain of dyspnoea, angina, and presyncope and/or syncope on exertion. At times syncope may occur on truly minimal exertion. The severity of symptoms on upright exertion do not necessarily correlate with the magnitude of the obstructive pressure gradient measured in the supine position, which is understandable particularly when the lability of the obstruction is taken into account. The severity of symptoms is often variable from day to day, as is the severity of the obstruction, which varies according to ventricular afterload (systolic blood pressure), preload, and contractility. The symptoms are often worse after a large meal or alcohol ingestion, when the obstruction is more severe. Many patients will also note presyncope on standing suddenly for the same reason. In our experience, patients with non-obstructive HCM present with these symptoms less frequently and usually the symptoms are milder,[5] but in some there is very severe disability resulting from left ventricular systolic and/or diastolic dysfunction. Congestive heart failure is rarely seen in HCM in normal sinus rhythm, but it may be seen with severe obstruction to outflow or severe systolic and/or diastolic dysfunction and is common in the presence of atrial fibrillation.

Although presyncope and syncope on exertion are common in obstructive HCM, it is

> **Obstructive versus non-obstructive HCM**
>
> - Extremely important to determine whether HCM is obstructive or non-obstructive
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> - If obstructive, is the obstruction subaortic or midventricular, or both?
>
> - If non-obstructive, is ventricular systolic function normal or impaired?
>
> - Non-obstructive HCM should be provoked to determine if latent (provocable) obstruction is present
>
> - There are important clinical signs that distinguish obstructive from non-obstructive HCM

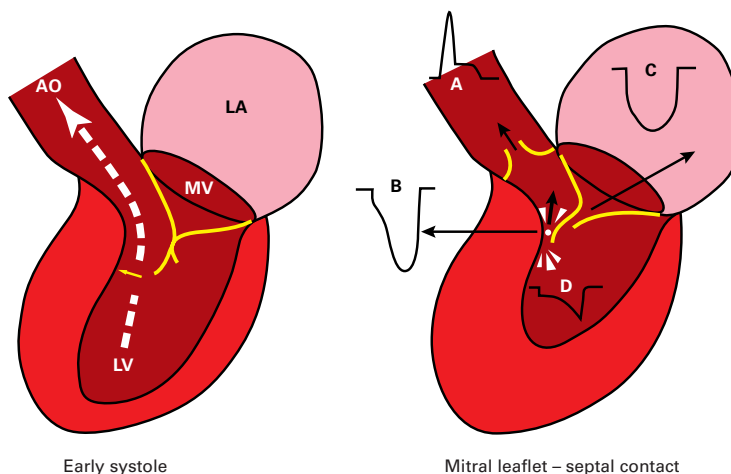Early systole   Mitral leaflet – septal contact

Figure 1. Diagram of the pathophysiology of the obstruction to outflow and mitral regurgitation in subaortic obstructive hypertrophic cardiomyopathy (HCM). Early systole (left): The left ventricular outflow tract is narrowed by the ventricular septal hypertrophy and the anterior displacement of the papillary muscles and the mitral leaflets. The point of coaptation of the elongated mitral leaflets occurs in the body of the leaflets, rather than at the tips, as is normal. That part of the anterior leaflet beyond the coaptation point is carried anteriorly and superiorly (systolic anterior motion, arrow) by venturi and/or drag forces and results in mitral leaflet–septal contact, causing the subaortic obstruction (indicated by the converging and diverging lines, right). Mitral leaflet–septal contact (right): The systolic anterior motion of the anterior leaflet results in a failure of coaptation of the mitral leaflets and the onset of mitral regurgitation, which is directed posteriorly into the left atrium, through the funnel shaped interleaflet gap. The length and mobility of the posterior leaflet may also affect the size of this gap, and hence the degree of mitral regurgitation. A, B, C, and D indicate Doppler velocity recordings throughout systole in the ascending aorta (A) (flow toward transducer), at the level of mitral leaflet–septal contact (B), in the left atrium (C), and near the apex of the left ventricle (D). In B, C, and D, flow is away from the transducer. Reduced forward flow in the presence of the obstruction is indicated by the shape of the aortic velocity waveform (A) and the smaller aortic arrow. Peak velocities recorded at B correlate accurately with the simultaneously measured pressure gradient, whereas late peaking velocities at D do not. AO, aorta; LA, left atrium, LV, left ventricle, MV, mitral valve. Adapted from Wigle et al.[7]

extremely important to recognise that these symptoms may also result from atrial and ventricular arrhythmias at rest or on exertion, or from failure of blood pressure to rise normally on exertion, even in non-obstructive HCM.[12] Thus, a history of palpitations, particularly rapid heart action when associated with presyncope/syncope, is an integral part of history taking.

Physical examination

Right ventricular involvement in HCM may be detected by a prominent A wave in the jugular venous pulse, that rises on inspiration and rarely by a right sided fourth heart sound, reflecting right ventricular diastolic dysfunction. A systolic ejection murmur along the high left sternal border often indicates subpulmonic or midventricular obstruction to right ventricular outflow.[5 7]

Left ventricular involvement is reflected by a variably displaced and forceful left ventricular impulse and a left sided fourth heart sound that is often palpable, reflecting impaired left ventricular relaxation. Patients with non-obstructive HCM either have no murmur or a faint grade 1/6 systolic murmur at the cardiac apex, that does not increase significantly with provocation. In patients with latent subaortic obstruction, the murmur at the apex is usually grade 1/6 to grade 2/6 in intensity, and increases to grade 3/6 with appropriate provocation such as amyl nitrite inhalation, assuming

> **Familial HCM**
>
> - Inherited as Mendelian dominant characteristic
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> - Related to mutations in sarcomeric proteins (a disease of the sarcomere)
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> - Taking a family history is important, particularly with regard to the occurrence of sudden cardiac death
>
> - Screening family members is also important
>
> - De novo mutations also cause HCM
>
> - HCM in the elderly may be familial, or non-familial and related to hypertensive hypertrophy and/or age related changes (sigmoid septum)

the upright posture from the squatting position or during the Valsalva manoeuvre. In patients with subaortic obstructive HCM at rest, the murmur at or just medial to the apex is grade 3/6 to 4/6 in intensity, and begins after the first heart sound. It is harsh and crescendo/decrescendo in character with radiation to the base of the heart, reflecting the obstruction, and to the axilla, reflecting the concomitant mitral regurgitation[7] (figs 1 and 2). In 20% of patients with subaortic obstructive HCM there may be independent abnormalities of the mitral valve (other than systolic anterior motion) that cause mitral regurgitation such as abnormal papillary muscle insertions, mitral valve prolapse or excessive fibrotic thickening of the anterior mitral leaflet, resulting from repeated mitral leaflet–septal contact.[5] In such cases there may also be a pansystolic murmur at the apex.

In addition to the louder apical murmur, there is an intriguing constellation of physical signs in subaortic obstructive HCM that are n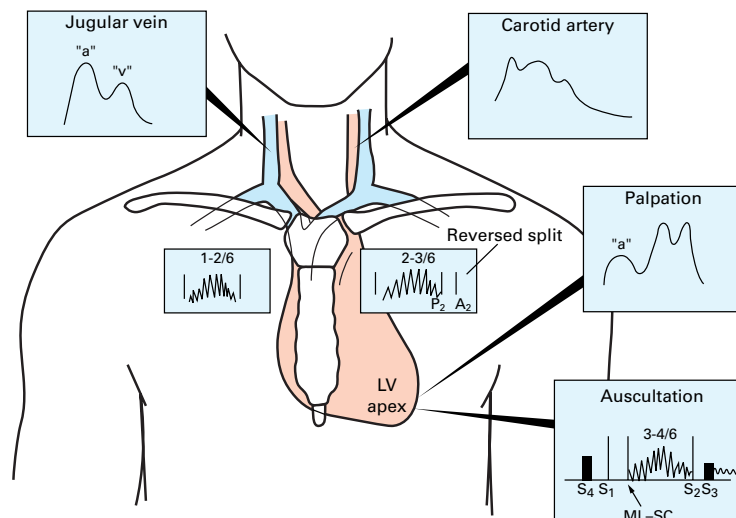ot seen in the non-obstructive form of the disease.[7] On palpation there is often a bifid (spike and dome) arterial pulse, which at times has been referred to as a bisferiens pulse incorrectly. A bisferiens pulse is seen in dominant aortic regurgitation. On palpation at the left ventricular apex, there is often a double systolic impulse, the first impulse coming before the onset of the obstruction, the second after. Frequently, there is a triple apex beat, resulting from a palpable left atrial gallop sound, plus a double systolic impulse. To appreciate the abnormalities on palpation over the left ventricular apex, it is extremely important that the patient be examined in the left lateral position (fig 2).

On auscultation in subaortic obstructive HCM, there may be a reversed or paradoxically split second heart sound when the obstruction is severe or in the presence of left bundle branch block. When the mitral regurgitation is significant, it is often accompanied by a mitral diastolic inflow murmur. Rarely a mitral leaflet–septal contact sound may also be heard (fig 2).

Patients with midventricular obstruction also have an apical systolic murmur, although it is usually softer, grade 2/6 to 3/6, than with subaortic obstruction. A bifid arterial pulse, double systolic apex beat or triple apex beat are not characteristic of midventricular obstruction and a mitral leaflet–septal contact sound is never found. If the obstruction is severe, there may be reversed splitting of the second heart sound. In midventricular obstruction, there is at times a very distinctive long mitral diastolic murmur, caused by the midventricular narrowing and asynchronous relaxation.[7]

In midventricular obstruction, the size of the obstructed apical cavity varies considerably. It may be quite large and haemodynamically significant or very small and more a manifestation of cavity obliteration with a small non-obliterated pocket of blood remaining at the apex. The syndrome of midventricular obstruction with apical infarction and aneurysm formation most often results from apical infarction in a patient with apical HCM in whom the non-infarcted hypertrophy at the midventricular level results in midventricular obstruction.[13]

Laboratory investigation

Patients referred with suspected HCM should have an ECG, a chest *x* ray, and a transthoracic echo Doppler examination on the initial visit.

The ECG in HCM may be normal with mild degrees of hypertrophy or show left ventricular hypertrophy and strain in the presence of extensive hypertrophy. Abnormal Q waves, which may mimic myocardial infarction, and which at times reflect septal hypertrophy, are a feature of the ECG in HCM, as are sharply negative T waves, particularly in precordial leads V3–V5 (giant T negativity syndrome) typical of apical HCM[14] (fig 3). Apical infarction may also be reflected in the ECG, and it is important to recognise that the ECG

Figure 2. Diagram showing the seven findings on physical examination that are found in subaortic obstructive HCM and are not present in non-obstructive HCM (see text). ML-SC, mitral leaflet-septal contact sound.

may be abnormal in HCM when echocardiography reveals no evidence of left ventricular hypertrophy.

The chest *x* ray may be normal or show left ventricular and/or left or right atrial enlargement, with or without vascular redistribution in the lungs. The aorta is typically small. A bulge on the left heart border, between the left atrial appendage and left ventricular apex, may reflect anterolateral wall extension of anteroseptal hypertrophy.

Transthoracic echo Doppler examination in HCM is undoubtedly the most important form of laboratory investigation. These combined techniques can determine the location and extent of hypertrophy, systolic and diastolic function, the presence and degree of systolic anterior motion, the severity of the subaortic and/or midventricular obstruction, the direction and degree of mitral regurgitation, the presence of additional mitral valve abnormalities, and left atrial size. The mitral regurgitation that results from systolic anterior motion of the anterior mitral leaflet is directed posteriorly into the left atrium (fig 1). If the mitral regurgitation is directed anteriorly or centrally, then additional abnormalities of the mitral valve such as abnormal papillary muscles or mitral valve prolapse should be suspected. Transoesophageal echo Doppler studies are particularly valuable in defining these additional mitral valve abnormalities and in distinguishing which type of obstruction is present in the left ventricle.[15 16] Patients who have no evidence of outflow obstruction at rest should routinely undergo appropriate provocation to determine whether there is echo Doppler evidence of latent or provocable obstruction.[5]

Previously, certain criteria of septal, apical, or free wall thickness were used to establish the diagnosis of HCM.[5] It is now recognised, as the result of molecular genetic–clinical correlations, that milder degrees of hypertrophy may also indicate HCM.

Ambulatory rhythm monitoring for detection of atrial and/or ventricular arrhythmias or conduction disturbances is of extreme importance in HCM once the diagnosis is established.

Nuclear angiography is very valuable in HCM to assess both systolic and diastolic ventricular function. Stress perfusion studies and positron emission tomography are important for detecting evidence of myocardial ischaemia or infarction.

Magnetic resonance imaging is of particular value in HCM when two dimensional echocardiography is unable to document the site and extent of hypertrophy, especially in apical HCM.

Heart catheterisation and angiography in HCM are usually reserved for diagnostic problems or when septal alcohol ablation or surgery are being considered in either type of obstructive HCM; they are also of value in the investigation of HCM with impaired systolic function with regard to the possibility of cardiac transplantation. The diagnostic accuracy of echo Doppler studies has dramatically lessened the need for invasive investigation in HCM. The precise role of electrophysiologic testing in
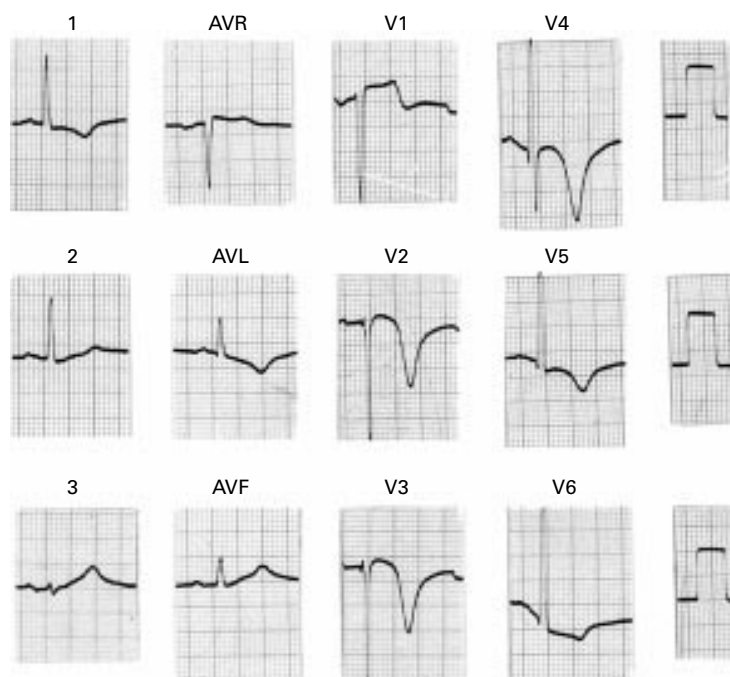

Figure 3. ECG from a patient with apical HCM showing the "giant T negativity syndrome"[14] (T waves more negative than 10 mm) in the precordial leads, usually maximal in V4. There is also voltage evidence of left ventricular hypertrophy.

the assessment of arrhythmia risk is as yet to be defined.

Genetic screening for HCM is prognostically important and undoubtedly will become more common once all the molecular genetic defects are defined and screening procedures simplified.

Assessment of risk

Assessment of risk of sudden cardiac death is an integral part of the work up of patients with HCM,[5 12 17 18] and will be addressed in a subsequent article in this series.

Investigation of HCM

- Echo Doppler examination is the most important diagnostic test in HCM and for determining the haemodynamic abnormalities present

- ECG may be abnormal when echo is normal, especially in the young

- Apical HCM most commonly suspected by an abnormal ECG (giant T negativity syndrome)

- Echo may fail to detect apical HCM in 10% of cases unless specifically looked for. Even then, magnetic resonance imaging may be required for definitive diagnosis

Special situations

Apical HCM

This form of HCM was originally described in Japan in the 1970s and is being recognised with increasing frequency in western populations.[14] Currently, we are following 120 patients with apical HCM, which represents a 9% incidence in our HCM clinic population of approximately 1300 patients (table 1). In approximately 50% of patients with apical HCM, the diagnosis will be first suspected or suggested by the abnormal ECG, with sharply inverted T waves in the lateral precordial leads (fig 3). A significant percentage of patients with apical HCM will present with atypical chest pain and the ECG abnormalities suggest ischaemia. These patients are often admitted to a coronary care unit if the admitting physician is not familiar with the ECG of apical HCM, which of course has voltage evidence of left ventricular hypertrophy, in addition to the sharply inverted T waves (fig 3). A second diagnostic characteristic of apical HCM is the spade shape of the left ventricle at end-diastole, which can be detected by echocardiography, angiography, or magnetic resonance imaging.[19 20] It is important to realise that apical hypertrophy can easily be missed on echocardiography unless great care is taken in the examination. Even then, magnetic resonance imaging is sometimes required to be definite about the diagnosis.

The prognosis in apical HCM is generally more favourable than in other forms of HCM, but these patients may suffer from apical ischaemia and/or infarction, which is often associated with ventricular arrhythmias, or atrial fibrillation, caused by left atrial enlargement resulting from left ventricular diastolic dysfunction.

Impaired systolic and/or diastolic dysfunction in HCM (end-stage HCM)

Progressive myocardial fibrosis from ischaemia and/or from fibrous transformation of the often abundant loose intercellular connective tissue in the myocardium[2 5 7] results in impaired systolic and/or diastolic function. In this stage of the disease, the left and right ventricular walls become thinner, the ventricles dilate, systolic function decreases, there is no longer evidence of outflow obstruction, and often mitral and tricuspid regurgitation in the presence of atrial fibrillation and congestive heart failure dominate the clinical picture. It is important to recognise this late stage of HCM because the negative inotropic drug therapy used for the treatment of obstructive HCM is now contraindicated, whereas treatments that would be contraindicated in obstructive HCM are now indicated—that is, afterload reduction, digitalis glycosides, and diuretics.[7] Patients with end-stage HCM are candidates for cardiac transplantation.

Atrial fibrillation

Atrial fibrillation in HCM is usually related to an enlarged left atrium, which most frequently

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Atrial fibrillation

- An important cause of morbidity: congestive heart failure, risk of systemic emboli, rarely syncope

- Almost always related to left atrial enlargement, which is most frequently seen in subaortic obstructive HCM (caused by concomitant mitral regurgitation) or in the presence of systolic and/or diastolic dysfunction

- In the presence of subaortic obstructive HCM, atrial fibrillation may lead to a mistaken diagnosis of mitral regurgitation because of the apical murmur

- Every attempt should be made to restore sinus rhythm pharmacologically or by cardioversion

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occurs in subaortic obstructive HCM caused by the concomitant mitral regurgitation; it may also be seen in non-obstructive HCM as the result of left atrial enlargement caused by diastolic dysfunction, particularly impaired left ventricular relaxation.[5 7] The onset of atrial fibrillation often precipitates left and right heart failure. When patients with subaortic obstructive HCM are seen in the emergency department with this arrhythmia, they are often misdiagnosed as mitral regurgitation because of the loud apical murmur. An incorrect diagnosis under these circumstances is to be avoided.

Conclusion

HCM is a heterogeneous disease, both genotypically and phenotypically, and is often a diagnostic challenge. Being aware of the diverse clinical and laboratory manifestations of HCM should avoid mistaken diagnoses in a disease that has been termed "The Great Masquerader".

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