Yamaguchi syndrome: a rare type of hypertrophic cardiomyopathy

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ABSTRACT

Apical hypertrophic cardiomyopathy, also known as Yamaguchi syndrome, is a rare variant of hypertrophic cardiomyopathy characterized by thickening of the apical segment of the left ventricle. Due to its non-specific symptoms and the limitations of standard echocardiography, it often remains undiagnosed. This article summarizes current literature regarding the epidemiology, pathophysiology, diagnosis, management, and prognosis of Yamaguchi syndrome. A narrative literature review was conducted using PubMed, Scopus, Web of Science, UpToDate, and European Society of Cardiology guidelines, analyzing studies published between 2016 and 2024, with emphasis on clinical presentation, imaging techniques, and risk assessment for sudden cardiac death. The syndrome is more common in Asian populations and is rarely reported in Europe and the Balkans. Electrocardiography typically reveals deep negative T waves in precordial leads, while cardiac magnetic resonance imaging remains the most accurate diagnostic method. Although the overall prognosis is generally favorable, some patients remain at risk for sudden cardiac death, particularly those with documented fibrotic involvement identified by late gadolinium enhancement. Management is usually conservative, with periodic follow-up and individualized decisions regarding the implantation of an implantable cardioverter defibrillator. Raising awareness of this rare variant, particularly in the Balkan region, is essential for timely diagnosis and optimal management.

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Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited disease of the cardiac muscle, characterized by hypertrophy not caused by hemodynamic overload. Within the spectrum of HCM, Yamaguchi syndrome represents a rare form that primarily affects the apical segment of the left ventricle.[1]

This form was first described in 1976 by Yamaguchi in Japanese patients and has since remained relatively unknown outside Asian populations.[2] Its prevalence in Western countries is very low (<2% of all HCM cases).[3] Often, this syndrome is not diagnosed in time due to the absence of cardiac outflow obstruction and its vague clinical presentation.[4]

This article aims to present a comprehensive review of the literature on Yamaguchi syndrome, including its epidemiological, pathophysiological, clinical, diagnostic, and therapeutic aspects, as well as the challenges it poses in daily clinical practice.

History and epidemiology

Yamaguchi syndrome is more prevalent in Asian populations, particularly in Japan, where it accounts for approximately 15% of all HCM cases.[5] In Western countries,

including Europe, apical HCM (ApHCM) is rare, accounting for approximately 3-10% of HCM cases.[6] This disparity may reflect both genetic background and diagnostic practices, particularly variation in the use of cardiac magnetic resonance (CMR) imaging, which has uncovered structural HCM features not evident on echocardiography.[7] Initially described as a "benign" form of HCM, later studies have shown that patients with myocardial fibrosis or ventricular arrhythmias may have an increased risk of malignant events.[8]

Pathophysiology and genetic basis

In Yamaguchi syndrome, myocardial thickening is restricted to the apical segment and typically produces a spade-shaped configuration on late gadolinium-enhanced CMR imaging.[9] Diagnosis may rely on a relative apical-to-basal wall thickness ratio ≥1.3 rather than absolute wall thickness alone.[10]

Unlike obstructive HCM, there is typically no significant increase in the outflow gradient from the left ventricle. However, mid-ventricular involvement and diastolic dysfunction are not uncommon. Genetically, though less studied than classic HCM, mutations have been identified in the *MYH7*, *MYBPC3*, and *TNNT2* genes, which encode sarcomeric proteins.[11]

Clinical presentation

Symptoms are often vague or mild, which contributes to delayed diagnosis.[12] The most frequently reported are non-typical chest pain, palpitations, and exercise-induced fatigue. Syncope and dizziness are less common but clinically significant, as they may indicate underlying arrhythmias or hemodynamic compromise.[12,13] ApHCM is also associated with a high prevalence of atrial fibrillation, which may remain undiagnosed until advanced stages.[14] Ventricular arrhythmias, although less common, have been reported and can occasionally present as sudden cardiac death (SCD) in previously asymptomatic patients.[15] In some patients, the presentation may be an incidental electrocardiography (ECG) showing giant negative T waves in leads V4-V6.[14] These ECG findings occur in up to 93% of patients, particularly in Asian cohorts, and are often the first clue to diagnosis in asymptomatic individuals.[4,5] Rarely, the patient presents with SCD as the first event.[16] Epidemiologic data reinforce that ApHCM accounts for up to 25% of HCM in Asian populations but only 1-10% in Western cohorts, highlighting both genetic and diagnostic differences.[17,18]

Diagnosis

Electrocardiography

The most characteristic findings are: i) deep negative T-waves (>10 mm) in precordial leads; ii) high-voltage QRS complexes; iii) ST segment depression (Figure 1).[19,20] These changes can be confused with subendocardial ischemia.

Transthoracic echocardiography

It has limited sensitivity in detecting apical thickening, especially in the absence of contrast. Contrast-enhanced or 3D echocardiography can be helpful (Figure 2).[21,22]

Cardiac magnetic resonance imaging

This is the most accurate diagnostic method for ApHCM because: i) it visualizes the characteristics "ace of spades" shape of the left ventricle; ii) it identifies myocardial involvement with late gadolinium enhancement (LGE) (fibrosis); iii) it assesses wall thickness and ventricular volume (Figure 3).[23]

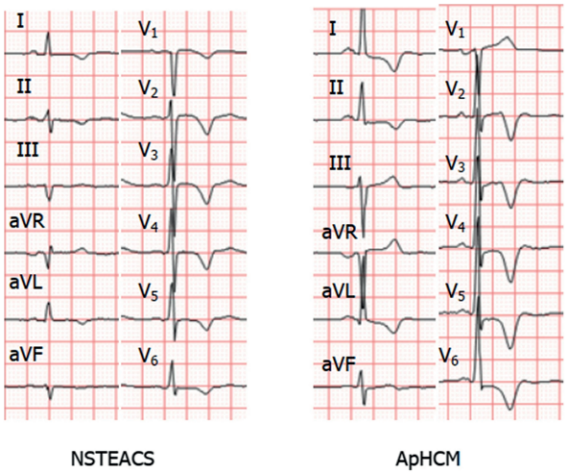

Figure 1. Representative electrocardiography of apical hypertrophic cardiomyopathy (deep negative T-waves in precordial leads). Reproduced from: Tao *et al.* (2020).[20]

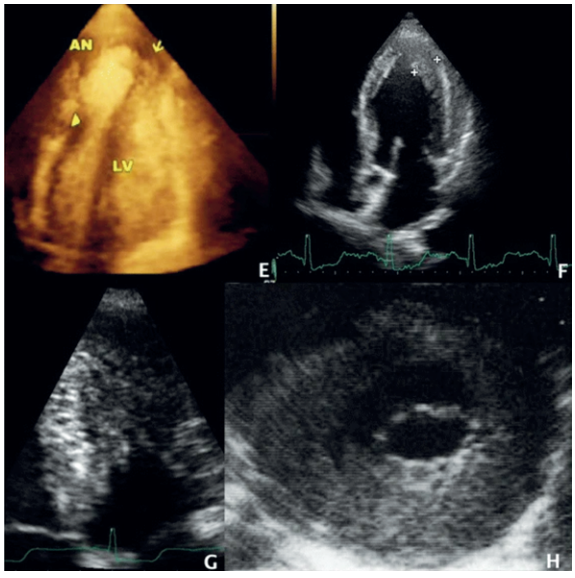

Figure 2. Apical hypertrophic cardiomyopathy (ApHCM) on transthoracic echocardiography: E) Imaging of left ventricle apical aneurysm; F) non-massive ApHCM; G) massive ApHCM with systolic cavity obliteration; H) asymmetric left ventricle posterior wall hypertrophy. Reproduced from: Parato *et al.* (2015).[22]

Other methods

Other methods include thoracic computerized tomography, myocardial scintigraphy to rule out ischemia, and Holter monitoring for subclinical arrhythmias.[24]

Differential diagnosis

Differential diagnosis includes coronary artery disease, Takotsubo cardiomyopathy (especially in the acute phase), cardiomyopathy with subendocardial fibrosis, cardiac amyloidosis, and left ventricular non-compaction cardiomyopathy.[25]

Prognosis

Previously considered a "benign form", but recent studies have shown: i) the risk for SCD is not zero, especially in patients with extensive LGE or with non-sustained ventricular tachycardia (NSVT);[26] ii) syncope, family history of SCD, and arrhythmias on Holter increase risk; iii) LGE on CMR is an important marker of fibrosis and elevated risk.[27]

Nevertheless, early studies suggested that most patients with ApHCM have a favorable long-term course with regular follow-up, as the risk of SCD and major adverse events is low compared to other HCM phenotypes.[28]

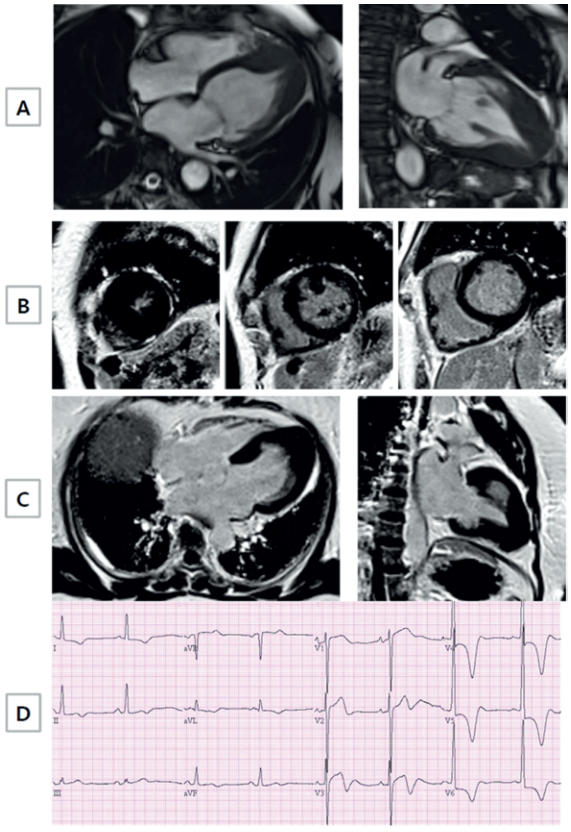

Figure 3. Classic "ace of spades" left ventricular cavity configuration in apical hypertrophic cardiomyopathy on cardiac magnetic resonance imaging (cine long-axis view). Reproduced from: Kim *et al.* (2012).[23]

Management and follow-up

Pharmacological treatment

Pharmacological treatment includes β-blockers or verapamil for symptom control and angiotensin-converting enzyme inhibitors if systolic dysfunction develops.[29]

Devices

An implantable cardioverter defibrillator (ICD) is indicated in patients with risk factors for SCD, whereas septal reduction surgery or ablation is not recommended.[26]

Monitoring and daily life

Moderate activity restrictions are recommended for patients with risk factors; periodic Holter and CMR are used for monitoring.

Challenges and future directions

Challenges and future directions in the context of ApHCM remain significant. At present, there are no specific data on the prevalence of ApHCM in the Balkan region, which limits regional understanding and comparison with global trends. Diagnosis continues to depend heavily on a high index of clinical suspicion, underscoring the risk of underdiagnosis or misclassification. To improve recognition and management, there is a clear need to establish national cardiology registries that would allow systematic data collection and long-term follow-up. Additionally, several emerging advancements hold promise for improving diagnostic accuracy and patient outcomes, including T1/T2 mapping techniques for the detection of fibrosis and cardiac inflammation, as well as strain imaging, which can identify subclinical dysfunction before overt disease manifestations occur.

Methods

This paper is a narrative review article aimed at analyzing and synthesizing current data related to apical cardiomyopathy, known as Yamaguchi Syndrome. A structured methodological approach was followed for its preparation. The databases used are PubMed, Scopus, Web of Science, UpToDate, and the European Society of Cardiology (ESC) guidelines, with a focus on articles published from 2016 onwards. The key words used are "Apical cardiomyopathy", "Yamaguchi Syndrome", "ECG", "Cardiac MRI".

Results

Based on the systematic review of scientific literature, these are the results.

The prevalence of Yamaguchi Syndrome is significantly higher in Asian populations (13-25%) compared to European populations (<2%).[5]

The most accurate diagnosis is achieved through CMR, which identifies apical hypertrophy and myocardial fibrosis using the LGE technique, which also serves as a marker for increased arrhythmic risk and myocardial fibrosis.[4,23,27]

ECG shows giant negative T waves in 93% of patients according to Japanese clinical cases, often in the absence of coronary artery disease.[14,19]

Apical myocardial fibrosis, identified through CMR and LGE, is associated with a higher risk of arrhythmias and SCD.[26,27]

The risk of SCD is lower compared to classic HCM but remains present in patients with additional risk factors such as LGE, syncope, or NSVT on Holter monitoring.[28,29]

Management is primarily conservative, involving the use of β-blockers, while the decision to implant an ICD should be based on a personalized risk assessment, in accordance with ESC recommendations.[26]

These findings highlight the need to increase diagnostic vigilance and promote a broader use of advanced imaging modalities in suspected cases of ApHCM, especially in countries where CMR imaging remains underutilized.

Discussion

Yamaguchi syndrome is a distinct and often underrecognized variant of HCM. Diagnosis requires a high degree of clinical vigilance, particularly when the ECG shows deep negative T waves in the absence of coronary artery disease.[26] Echocardiography may not be sufficiently sensitive to visualize apical hypertrophy, especially when apical visibility is limited; therefore, CMR remains the diagnostic gold standard.

The role of LGE in assessing the risk for SCD is increasingly emphasized. An LGE burden exceeding 15% of myocardial mass is associated with a significantly elevated risk of arrhythmias. ESC guidelines recommend the use of the SCD risk model for all patients with HCM, including those with ApHCM, although the model is less validated in this subgroup.[16]

Recent systematic reviews and meta-analyses have consolidated ApHCM as a morphologically distinct phenotype, characterized by the classic "spade-shaped" left ventricular configuration and a clinical trajectory that diverges from obstructive HCM.[30] Long-term follow-up studies now demonstrate that ApHCM patients generally have lower all-cause mortality and heart failure hospitalization rates compared to other HCM variants, although the risk of arrhythmias and SCD persists in subsets with significant fibrosis or documented NSVT.[18,31]

In countries such as Albania and Kosovo, where CMR availability is limited and diagnosis often relies solely on ECG and echocardiography, there is a high risk of underdiagnosing this syndrome. This underscores the need for continuous medical education and a multidisciplinary diagnostic approach.[4]

Taken together, these findings emphasize the importance of expanding access to CMR imaging in the Balkans, not only for diagnosis but also for accurate risk stratification, as failure to detect fibrosis may underestimate SCD risk. Moreover, establishing regional registries would help clarify prevalence and outcomes in non-Asian populations.[17,18]

Conclusions

Yamaguchi syndrome is a rare and often underappreciated variant of HCM, with diverse clinical presentations and diagnostic challenges. CMR imaging has significantly enhanced our ability to identify this condition. Increased awareness, particularly in the Balkan region, and individualized medical follow-up are essential to prevent adverse events and improve long-term outcomes.

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