A 16-year-old boy was brought to the hospital when he complained of chest pain while at a basketball game. In the emergency room, he was noted to have a wide complex tachycardia. The ECG at presentation is shown in Figure 1. He was cardioverted after administration of 150 mg of intravenous amiodarone. His ECG after cardioversion is shown in Figure 2. His physical examination and developmental evaluation were significant for obesity, synophrys, mild fifth digit clinodactyly, and subnormal intelligence. Cardiac magnetic resonance imaging with contrast showed massive left ventricular hypertrophy (LVH), with preserved ejection fraction, and several areas of delayed hyperenhancement in the subendocardium. Cardiac catheterization showed no obstructive coronary artery disease or anomalous coronary arteries. What are the diagnostic considerations for this constellation of findings of massive LVH, subendocardial necrosis, and abnormal ECGs?

Discussion

The ECG in Figure 1 displays a wide complex tachycardia, with a right-bundle branch block morphology with a QRS complex duration >120 ms. A wide complex tachycardia with a right-bundle branch block morphology could be secondary to ventricular tachycardia originating from the left ventricle or a preexcited tachycardia in the presence of a left-sided bypass tract. However, the QS complex in lead V₆ rules out a left-sided atrioventricular bypass tract, because such bypass tracts do not have the left ventricle apex as their ventricular insertion site, which is necessary to produce a QS complex in V₆. A left-sided nodofascicular bypass tract with insertion in the distal His-Purkinje system can produce Q complexes in lead V₆, but these are extraordinarily rare and occur more frequently on the right side. Initial R wave in lead aVR, a QS complex in lead V₆, and northwest axis that is completely different from the preexcited QRS complex in sinus rhythm seen in Figure 2 argue for ventricular tachycardia being the mechanism of the tachycardia in Figure 1. Thus, the tachycardia depicted in Figure 1 is diagnosed as ventricular tachycardia. Figure 2 shows an ECG consistent with sinus rhythm, ventricular preexcitation, and a transition to R/S>1 in lead V₂ with a relatively normal axis. Using the algorithm suggested by Arruda et al, the bypass tract causing preexcitation in this ECG will be localized to the anteroseptal region. However, fasciculoventricular bypass tracts (FVBT) share electrocardiographic features of both anteroseptal and midseptal pathways. Sternick et al systematically analyzed the value of (1) ECG frontal plane QRS and delta-wave axis; (2) QRS width; (3) R/S ratio in lead III; and (4) precordial lead transition to R/S>1 in distinguishing FVBT from anteroseptal and midseptal bypass tracts. They reported that transition to R/S>1 in the precordial leads occurred mainly in lead V₂ in patients with manifest fasciculoventricular pathways, V₃ in midseptal pathways, and V₄ in anteroseptal bypass tracts. However, it should be noted that surface ECG cannot reliably differentiate FVBT from an anteroseptal or midseptal bypass tracts. Thus, a definitive distinction can only be made with an electrophysiological study.

Wide complex tachycardia in our patient was secondary to ventricular tachycardia in the setting of structural heart disease. We performed an electrophysiological study to elucidate the cause of preexcitation, and the salient findings are, hereby, presented. Baseline intervals are as follows: PR interval, 157 ms; QRS duration, 140 ms; atrial-His interval (AH), 59 ms; and His-ventricular interval, 14 ms. The response to an atrial extrastimulus is shown in Figure 3. Ventricular preexcitation was absent once the atrioventricular nodal effective refractory period was reached. The response to His pacing is shown in Figure 4. Double ventricular extrastimuli at a drive cycle length of 600 ms and coupling intervals of 215 and 230 ms resulted in ventricular tachycardia with right-bundle branch block morphology and left-axis deviation, with a cycle length of 300 ms, and it terminated spontaneously. We were not able to induce the same wide complex tachycardia recorded in Figure 1. There was no ventriculoatrial conduction at baseline or during ventricular tachycardia.

Fixed preexcitation with variable AH intervals, dependence on atrioventricular nodal conduction, and preexcitation with junctional ectopy or His extrasystoles are pathognomonic features of FVBT. FVBT are interesting because their ECG appearance may simulate anteroseptal or midseptal accessory pathways, but they have never been proven to participate in tachycardia, except as bystanders. Wide complex tachycardia morphology that is different from preexcitation argues for ventricular tachycardia.

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being the mechanism of the tachycardia in our patient and is probably caused by hypertrophic cardiomyopathy and diffuse scarring. As fasciculoventricular tracts are not true atrioventricular bypass tracts and do not participate in reciprocating tachycardia, ablation of these tracts is not recommended and, thus, not pursued in our patient. However, such variant forms of hypertrophy and scarring in association with preexcitation engendered suspicion for inherited forms of preexcitation. We, therefore, present a brief overview of genetic mutations that are known to result in Wolff–Parkinson–White syndrome in association with left ventricular hypertrophy.

Danon Disease
Danon disease is a malignant phenocopy of hypertrophic cardiomyopathy with multisystem involvement caused by lysosome-associated membrane protein 2 mutations. In addition to severe LVH, patients have skeletal myopathy, hepatic involvement, and mental retardation. ECGs in patients with Danon disease frequently demonstrate preexcitation. A representative ECG from a patient with Danon disease who underwent orthotopic heart transplantation at the age of 16 is shown in Figure 5.

Fabry Disease
Anderson-Fabry disease is an X-linked recessive disorder because of α-galactosidase A deficiency. Severe LVH resulting in heart failure, atrial fibrillation, and conduction system diseases is known to be associated with Fabry disease.

PRKAG 2 Mutation
The genetic mutation associated with familial Wolff–Parkinson–White syndrome was initially described in a large French-Canadian family in 1986. In this family, the members who were affected showed clinical findings that consisted of preexcitation, conduction abnormalities, and cardiac hypertrophy. The syndrome has an autosomal dominant mode of inheritance. Genetic linkage analysis identified the putative locus to be on chromosome 7 (7q3), and the gene was subsequently identified to be \( \text{PKRAG2} \), which encodes the \( \gamma-2 \) subunit (noncatalytic subunit) of 5-AMP-activated protein kinase. Since this initial discovery, 5 more mutations in the same gene have been identified. All mutations have been missense mutations in \( \text{PKRAG2} \). \( \text{PKRAG2} \) mutation is associated with LVH and ventricular preexcitation, most notably with fasciculoventricular pathways. LVH in patients with \( \text{PKRAG2} \) is caused by glycogen storage in the myofibrils, with a reported incidence of 26% to 74%. It is possible that the true incidence of these mutations is underestimated and that many cases are wrongly diagnosed as idiopathic hypertrophic cardiomyopathy. Some cases of patients with fasciculoventricular pathways and LVH without genetic assessment have also been reported. \( \text{PKRAG2} \) may play a role in the development of annulus fibrosus, and malfunction of the gene, by causing prominent structural disruptions with extensive arborization, may explain the remarkably high incidence of multiple atrioventricular accessory pathways seen in patients with the \( \text{PKRAG2} \) mutation. In addition to the presence of bypass tracts, high incidence of conduction abnormalities and typical atrial flutter have also been
reported in patients with \textit{PRKAG2} mutations.\textsuperscript{15} We have encountered a patient with \textit{PRKAG2} mutation, who has an anteroseptal pathway as the only route of antegrade conduction from the atrium to the ventricle. Interestingly, this patient also developed cavotricuspid isthmus-dependent flutter with rapid conduction via the accessory pathway. This flutter was successfully ablated.

\textbf{Mitochondrial Disorders That Are Maternally Inherited}

Leber hereditary optic neuropathy (LHON) is one of the most common mitochondrial genetic diseases, with an estimated prevalence of 1 in 25,000 in North East England.\textsuperscript{16} This is characterized by acute or subacute functional impairment in both eyes, mostly in men during early adulthood or midlife.\textsuperscript{17} The mitochondrial DNA mutations 11778G$>$A, 3460G$>$A, and 14484T$>$C are found in 95\% of all LHON cases. Prolonged QT interval, cardiac conduction abnormalities, and preexcitation have been described in these patients.\textsuperscript{14-20} Structural abnormalities, including hypertrophic cardiomyopathy and abnormal left ventricular trabeculation, have also been described in patients with LHON.\textsuperscript{20,21} Electrocardiographic manifestation of preexcitation has been shown to be common not just in the Finnish population as initially thought, but also in other ethnic groups afflicted with LHON.\textsuperscript{22} Patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome caused by mitochondrial DNA 32343 A$>$G mutations have also been found to be afflicted with severe cardiac hypertrophy in association with preexcitation.\textsuperscript{23-25} There is no proven curative treatment for mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome, and the long-term life expectancy of patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome is dependent on the organ systems involved.

\textbf{Tuberous Sclerosis}

Tuberous sclerosis is an autosomal dominant disease with frequent occurrence of cardiac rhabdomyomas. Clinical features include tumors in various organs that result in a variety of clinical manifestations that include intractable epilepsy and malignant arrhythmias. The putative genetic loci have been identified on chromosomes 9 and 16.\textsuperscript{26,27} Cardiac rhabdomyomas are thought to contribute to the occurrence of accessory pathways, but cases of tuberous sclerosis and Wolff–Parkinson–White syndrome without cardiac rhabdomyomas have also been reported.\textsuperscript{28}

\textbf{Pompe Disease}

Pompe disease is an autosomal recessive disorder that results from the deficiency of acid $\alpha$-glucosidase, a lysosomal hydrolase. Three major forms of the disorder are recognized: infantile, juvenile, and adult onset. The infantile form usually presents by the age of 6 months and is marked by a progressive and rapidly fatal course. Recombinant human $\alpha$-glucosidase treatment has shown some promise in the treatment of this disease.\textsuperscript{29} The association of Pompe disease with preexcitation was reported as early as 1978.\textsuperscript{30} A synopsis of these genetic preexcitation syndromes is presented in the Table.

Careful electrophysiological analysis (when indicated) should be undertaken to demonstrate the presence of an accessory pathway in genetic preexcitation syndromes because preexcitation pattern in ECG in patients with storage disorders does not automatically imply the presence of an accessory pathway as demonstrated elegantly by Drs Bulkley and Hutchins in 1978,\textsuperscript{30} and more recently by Sternick et al\textsuperscript{15} in 2 families with \textit{PRKAG2} mutations—the so-called familial pseudopreexcitation syndrome. In these patients, enhanced atrioventricular nodal conduction with conduction disturbances in the His-Purkinje system resulted in short PR intervals in association with bundle branch block patterns on ECG.
Danon disease was ruled out by molecular diagnostics, and further testing was advised to the patient. The patient and his family refused to undergo further testing; so the ultimate molecular diagnosis in this case remains elusive, and Fabry disease can be treated with biweekly infusions of the deficient enzyme Atorvastatin and atriofascicular bypass tracts are more often affected.

In contrast to the excellent long-term prognosis of patients with accessory pathways without structural heart disease and known genetic mutations, those with accessory pathways and genetic mutations that cause multisystem disease have a guarded prognosis. Patients in whom preexcitation is associated with unexplained cardiac hypertrophy should be evaluated for genetic mutations, and a multidisciplinary treatment plan should be instituted, should a mutation that affects multiple organ systems be discovered.

Disclosures

None.

References


Table. Genetic Disorders With Preexcitation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Inheritance</th>
<th>Genetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danon</td>
<td>LVH, CHF, Skeletal myopathy, Hepatic involvement, Mental retardation</td>
<td>X-linked</td>
<td>LAMP2 mutations</td>
<td>Men more frequently than women</td>
</tr>
<tr>
<td>Fabry</td>
<td>LVH, CHF, Atrial fibrillation, Conduction system disease</td>
<td>X-linked</td>
<td>α-Galactosidase A deficiency</td>
<td>Fabry disease can be treated with biweekly infusions of the deficient enzyme</td>
</tr>
<tr>
<td>LHON</td>
<td>Acute or subacute impairment in both eyes, Prolonged QT interval, Cardiac conduction abnormalities, Hypertrophic cardiomyopathy, Abnormal left ventricular trabeculation</td>
<td>Matrilineal</td>
<td>mtDNA mutations 11778G&gt;A, 34605&gt;G, 14484T&gt;C</td>
<td>Men are more often affected</td>
</tr>
<tr>
<td>MELAS</td>
<td>Encephalopathy, Unexplained lactic acidosis, Stroke-like episodes, Diabetes mellitus</td>
<td>Matrilineal</td>
<td>mtDNA 32343 A&gt;G</td>
<td>Men are more often affected</td>
</tr>
<tr>
<td>Pompe</td>
<td>Infantile form, Cardiomegaly, cardiomyopathy arrhythmias, hypotonia, respiratory distress, skeletal myopathy, feeding difficulties, and failure to thrive Late-onset form, Impaired cough, hypotonia, progressive myopathy, delayed motor milestones, difficulty with deglutition and mastication, and reduced vital capacity</td>
<td>Autosomal</td>
<td>Deficiency of acid α-glucosidase Mutation is localized to chromosome 17</td>
<td>Recombinant human α-glucosidase treatment has shown some promise in the treatment of this disease</td>
</tr>
<tr>
<td>PRKAG2 mutation</td>
<td>Conduction abnormalities, severe LVH, subendocardial ischemia secondary to massive LVH, and atrial flutter</td>
<td>Autosomal</td>
<td>Chromosome 7 (7q3)</td>
<td>Conduction abnormalities mandate careful evaluation of AV nodal and His-Purkinje function before ablation of SVT High prevalence of fasciculoventricular bypass tracts</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Cardiac rhabdomyomas, Astrocytoma of the brain, Lymphangioleiomyomatosis of the lung, Phakoma and colobomas of the eyes, Angiomyolipomas of the kidneys, Café aulait spots on the skin</td>
<td>Autosomal</td>
<td>TSC 1: chromosome 9, TSC 2: chromosome 16</td>
<td>Surgical treatment might be necessary to cure intractable epilepsy and malignant arrhythmias</td>
</tr>
</tbody>
</table>

LVH, indicates left ventricular hypertrophy; CHF, congestive heart failure; LAMP2, lysosome-associated membrane protein; LHON, Leber hereditary optic neuropathy; mtDNA, mitochondrial DNA; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; AV, atrioventricular; SVT supraventricular tachycardia; TSC, tuberous sclerosis complex.


Editor's Perspective

In this installment of the Teaching Points series, Koneru et al describe in a clear and elegant fashion one of the more complex areas related to accessory pathway recognition and ablation—syndrome accessory pathways. In this scenario, the accessory pathway is one manifestation of a disease process. Occasionally, accessory pathway-related arrhythmias are the presenting feature of the underlying syndrome (Fabry disease and cytidine 5’-monophosphate [CMP]-kinase defects). Accessory pathway ablation is generally a straightforward procedure; however, the electrophysiologist needs to be aware of a systematic approach to dealing with the unusual, difficult accessory pathway.

Appearance of An Antegrade Conducting Accessory Pathway

Antegrade (AV) bypass tract connects the atrial and ventricular myocardium via a route other than through the AV node. Koneru et al describe a case where a pattern consistent with preexcitation is because of a fasciculoventricular tract. Here, the AV node is the only connection between the atrium and ventricle. However, a gap in the fibrous insulation separating the HS bundle and proximal bundle branches, allows conduction to the myocardium. Thus, the HV interval is short, and there is slurring of the upstroke of the QRS. These connections do not cause arhythmias, yet, can lead to evaluation because of the preexcitation pattern noted on a resting EKG. Because conduction is only through the AV node, decremental atrial pacing, differential site atrial pacing, and modulation of AV node conduction (adenosine, calcium channel antagonists, and exercise) do not change the extent of preexcitation or the HV interval. It is important to be aware of this entity and know that no ablative or other therapy is required.

Pseudoelectrocardiogram Without an Accessory Pathway

The electrocardiogram can give the appearance of preexcitation with certain myocardial disorders. The best recognized is the pseudoelectrocardiogram seen in some patients with hypertrophic cardiomyopathy. The PR interval is short with a flattened QRS onset mimicking a delta wave.1 Electrophysiologic study reveals conduction only through the AV node.

Confusing Retrograde AV Node–Dependent Activation Patterns

Because the coronary sinus (CS) itself has functioning atrial myocardium with variable connections to the left atrium, eccentric atrial activation may be seen during ventricular pacing or AV node reentry, in the absence of an accessory pathway.2 Typically, retrograde atrial activation is typically via the fast pathway from the AV node. From the fast pathway exit, posterior to the tendon of Todaro, the activation wavefront may take one of several routes to reach the CSs. The simplest is to traverse or skirt the Eustachian ridge in the right atrium itself. However, in some patients activation proceeds leftward to the left atrium and then to the CS through a left atrium connection. These connections may be discrete and present predominantly in the mid or distal portion of the CS. Thus, the CS records show a distal to proximal activation sequence (eccentric activation). This situation can be easily clarified by noting that a catheter placed in the fast pathway region shows retrograde activation and, in the majority of CS recording showing left atrial myocardium capture, the CS activation is eccentric.

Decremental Conduction

While in general retrograde AV nodal conduction is decremental while pathway conduction is not, important exceptions exist. In permanent form of junctional reciprocating tachycardia and some patients with Ebstein anomaly, retrograde pathway conduction is decremental and can be mistaken for nodal conduction. In children or during isoproterenol administration, the decremental conduction in the AV node may be hard to detect, making one suspect an accessory pathway.

Parasitization Pacing

Parasitization pacing is among the most direct and useful maneuvers to distinguish retrograde pathway conduction from AV nodal conduction. Although many important variant responses have been described and analyzed, occasionally a pathway may be halfway diagnosed or missed altogether. High output pacing from the right septum can capture left ventricular myocardium and result in early activation of the atrium via an accessory pathway, whereas lower output capture takes longer to reach the left ventricle, creating confusing patterns of shorter VA time with QRS narrowing, suggesting AV nodal conduction, despite the presence of an accessory pathway. Similarly high- and low-output pacing too close to the annulus may result in atrial myocardial capture such that the ventricular activation interval remains fixed independent of the output pacing, falsely suggesting a septal accessory pathway.

Premature Ventricular Complexes Placed During Tachycardia

Premature ventricular complexes placed at the time of His bundle refractoriness during supraventricular tachycardia that preexcites the atrium without a change in the atrioventricular conduction sequence may be observed. However, rarely, in patients with AV node reentry who have a bystander retrograde conducting nodoventricular tract, a similar response can occur during AV nodal reentrant tachycardia. The premature ventricular complexes conduct over the nodoventricular tract to reset the AV nodal reentry.

Multiple Pathways

When more than 1 accessory pathway is present during tachycardia, activation changes from varying pathway contribution to atrial activation make mapping and ablation far from straightforward. With multiple pathways, ablation of the pathway that is a bystander during tachycardia fails to terminate tachycardia or block VA conduction but produces a change in activation sequence. The change in activation may be subtle, falsely suggesting an ineffective radiofrequency ablation attempt. However, it is important to deliver an adequate lesion to permanently ablate this pathway, which will otherwise remain and may be responsible for tachycardia at another time. Further mapping is then performed to guide ablation of the second pathway. An important clue that the trainees should look for and keep in mind is unexpectedly early activation at a site distant to the right atrium. In other words, when a left-sided pathway is present and responsible for AV reentrant tachycardia, activation should be significantly later on the septum and even later on the right free wall. If near simultaneous or unexpectedly early activation occurs at these disparate sites, additional bystander pathways should be suspected.

Prior Ablation

Exact identification of the original encoded electrogams is essential when ablating accessory pathways. For example, with retrograde pathway activation, the pathway potential and early atrial electrograms are used to decide where to ablate. In patients with prior failed ablation attempts, mapping is often complicated by scar and highly fragmented signals near the pathway because the prior ablation lesions. Simple associative and dissociative maneuvers help distinguish between nonrelated fragmented signals and electrogams directly related to pathway activation (pathway potential). For example, with atrioventricular pathway conduction, a fragmented late atrial electrogram may be mistaken for early atrial activation or a pathway potential. However, it is noted that the fragmented electrogams stay with the atrium when atrial pacing produces the AV block. However, if these early signals are no longer seen when AV block or pathway block is induced then these electrogams are not atrial and may represent early ventricular activation or a pathway potential.

Accessory Pathways in Unusual Locations

Accessory pathways may involve the myocardium of the CS and its tributaries, thus, require venous or epicardial mapping and ablation for success. Rarely, the accessory pathway is a myocardial connection between an atrial appendage and the epicardial adjacent ventricular myocardium. Here, the mapping and ablation catheter needs to be manipulated into the appendage or target the pathway from the epicardium.

Conclusion

Ablation for accessory pathways is curative in the majority of patients. When pathway mapping and ablation are difficult, the trainee needs to appreciate the possible reasons for difficulty and have a systematic approach to recognize the problem and identify the pathway for ablation. Such an approach should include recognizing syndromic associations with accessory pathways and mimics of accessory pathways, and employ maneuvers to identify multiple pathways, and correctly identify accessory pathway potentials. Further, the electrophysiologist should be aware that any or all of these causes for difficulty with ablation may occur for pathways in unusual locations.

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Rare Forms of Preexcitation: A Case Study and Brief Overview of Familial Forms of Preexcitation
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