Polymorphic catecholergic ventricular tachycardia

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Abstract
Identified in 1978, catecholaminergic polymorphic ventricular tachycardia mainly occurs in children over 3 years old with apparently healthy hearts. It is a primary dysrhythmia usually discovered during the work-up conducted after syncope with or without seizure. Syncopes mainly occur during exertion or emotional experiences. The electrocardiogram is normal (particularly the QT interval). During exercise or acceleration of the sinus rhythm, stereotyped and repetitive ventricular extrasystoles appear: first isolated and monomorphic, they become polymorphic and occur in salvos, with bidirectional ventricular tachycardia. Ventricular arrhythmia may be very rapid and interspersed with bursts of supraventricular or junctional tachycardia. During the paroxysms, torsade en pointes and ventricular fibrillation may appear and sometimes revert spontaneously. The same arrhythmia can be induced by stress tests or injecting small doses of isoprenaline. Patients are treated with powerful beta-blockers with delayed action. The spontaneous outcome is poor: half of the untreated patients die before age of 20 years. The disorder, recently assigned to the group of rhythm channelopathies, is familial in 1/3 cases. Somes cases are associated with abnormal transmembrane calcium transport (a mutation of the cardiac ryanodine-receptor gene, RyR2*, has been found in several families).*

Keywords
Ventricular tachycardia, arrhythmia, sudden death, torsade de pointes, long QT syndrome, ventricular fibrillation, calcium channelopathy

Name of the disease and its synonyms

- Catecholaminergic polymorphic ventricular tachycardias (CPVT)
- Isolated cases or small series of patients have been described in the literature using the following terms:
- Syncopal paroxysmal tachycardia
- Malignant paroxysmal polymorphic ventricular tachycardia

- Multifocal ventricular premature beats
- Paroxysmal ventricular fibrillation
- Bidirectional tachycardia
- Double tachycardia induced by catecholamines
- Syncopal tachyarrhythmia
- Familial polymorphic ventricular tachycardia
- Catecholamine- or exercise-induced polymorphic ventricular tachycardia

Names of excluded diseases
By definition, the following entities are excluded from the differential diagnosis :
- Long QT syndromes: Jervell & Lange–Nielsen syndrome (autosomal recessive with associated deafness), Romano–Ward syndrome (autosomal dominant with no deafness)
- Brugada syndrome
- Arrhythmogenic right ventricular dysplasia
- Torsade-de-pointes syndromes with short coupling interval

Diagnostic criteria/Definition
CPVT is a primary arrhythmia seen in children over 3 years old without evident cardiopathy; it provokes prolonged syncopes, with or without seizures, often triggered repeatedly and reproducibly by physical exertion, emotional upheavals or the injection of small doses of isoprenaline chlorhydrate. The standard electrocardiogram is normal, but sinus bradycardia is common at rest, as is the left QRS axis for this age (1/2 patients). With physical exercise, for a sinus rhythm threshold > 130/minute, ventricular extrasystoles appear: first alone and monomorphic, then polymorphic and in salvos. During these polymorphic ventricular tachycardia attacks, interspersed bidirectional ventricular tachycardia salvos, or supraventricular or atrioventricular (nodal) and His–Purkinje system tachycardia bursts are seen. The arrhythmia can degenerate at any time into torsade de pointes or ventricular fibrillation which can (but does not always) revert spontaneously.

Differential diagnosis
By definition, the hearts of these children are anatomically normal and the affected individuals are *a priori* free of any known metabolic disease. Before advancing the diagnosis, the following must be eliminated:
- Cardiomyopathy (echocardiography)
- Metabolic disease (biological work-up)
- Pheochromocytoma (catecholamine dosage)
- Arrhythmogenic right ventricular dysplasia(angiography or scintigraphy)
- Brugada syndrome (electrocardiogram, provocation test)
- Torsade de pointes with short coupling interval (electrocardiogram aspect)
- Long QT syndromes (genetic investigation). But some borderline forms exist in which both prolonged QT intervals and effort- or isoprenaline chlorhydrate-induced reproducible CPTV are seen.

Frequency
In our experience, CPTV is a rare rhythm disorder, often misunderstood, that occurs about half as frequently as long QT syndromes. The rhythm disorder is not seen in newborns (in contrast to long QT syndromes). The effort-induced ventricular extrasystoles and syncopes can appear later during childhood (after 3 years).

Clinical description
Diagnosis is primarily derived from medical history taking after the occurrence of syncopes, with or without seizures, triggered by physical exertion or emotional upheavals. Loss of consciousness can be long and accompanied by sphincter release (urinary and anal). Neurological sequelae are possible after a more-or-less prolonged coma. Sudden death is the natural outcome in the absence of adapted therapy. Electrocardiogram anomalies can be seen after paroxysms and these children are often treated for epilepsy for several months or even years before the correct diagnosis is made.

Management/treatment
As soon as diagnosis is made, it is imperative that treatment with a beta-blocker be started. We prefer nadolol because of its long half-life, allowing a single dose per day (80–160 mg in teenagers).
Under treatment, sinus brachycardia is sometimes more severe. Ventricular extrasystoles persist, usually for sinus rhythms exceeding 130/minute. In contrast, the syncopes disappear as long as the medication is taken regularly. The beta-blocker is life-long therapy. Particularly severe forms can justify the implantation of a cardioverter defibrillator.

Etiology
This primary rhythm disorder was recently assigned to the group of rhythm channelopathies, along with long QT syndromes. Indeed, several teams have demonstrated a calcium-channel abnormality in affected families associated with a dominant mutation in the cardiac ryanodine-receptor gene (*RyR2*) localized to chromosome 1q42–43. More rarely, the disorder has been linked to a recessive mutation on chromosome 1p13–21.

Biological diagnostic method
None exists.

Genetic counseling

The existence of familial forms for 1/3 patients justifies the undertaking of a complete familial investigation at the time of the first diagnosis. An autosomal dominant transmission has been established in some families bearing a mutation on chromosome 1q42–43. Recessive inheritance of a mutation on chromosome 1p13–21 has also been demonstrated in a Bedouin tribe.

Unresolved questions and comments

This severe primary rhythm disorder that occurs in children over 3 years old is probably more misunderstood than rare. This misunderstanding can lead to dramatic accidents during sporting events, especially swimming. The beta-blocker treatment is prescribed for the patient's entire life without interruption. The progress made in molecular genetics have provided a better understanding of this arrhythmia, as well as the possible similarities (and differences) between CPTV and long QT syndromes or right ventricular dysplasia. Familial genetic analysis should include repeated monitoring of children *a priori* disease-free, because electrical signs can appear late in childhood or during young adulthood.

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