[Frontiers in Bioscience E1, 519-527, June 1, 2009]

# Cardiac conduction disorders in children

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## 1. ABSTRACT

Conduction disorders result in cardiac arrhythmias that may be fatal. Histiocytoid cardiomyopathy, Arrhythmogenic right ventricular dysplasia, Isolated noncompaction of the left ventricle, Long QT syndrome (LQTS) and Brugada syndrome, are all well described. Congenital short QT syndrome is a new familial primary electrical disease of the heart, which is characterized by abnormally short QT interval and paroxysmal atrial and ventricular tachyarrhythmias, including sudden cardiac death. An autosomal dominant mode of inheritance has been suggested. Catecholaminergic polymorphic ventricular tachycardia is an inherited disease and occurs in the absence of structural heart disease or known associated syndromes. Although the histological appearance of some of these disorders may be diagnostic, molecular analysis is necessary to define clearly the particular type of cardiomyopathy. The spectrum of the cardiac conduction disorders is reviewed and discussed.

## 2. INTRODUCTION

Conduction disorders result in cardiac arrhythmias that may be fatal. Inherited diseases in which arrhythmias and sudden death are prominent features include histiocytoid cardiomyopathy, arrhythmogenic right ventricular dysplasia, isolated noncompaction of the left ventricle myocardium, long QT syndrome, Brugada syndrome, congenital short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. Although the histological appearance of some of these disorders may be diagnostic, molecular analysis is necessary to define clearly the particular type of cardiomyopathy.

## 3. CARDIAC CONDUCTION DISORDERS IN CHILDREN

### 3.1. Histiocytoid (oncocytic) cardiomyopathy

Histiocytoid (oncocytic) cardiomyopathy is characterized by cardiomegaly, incessant ventricular

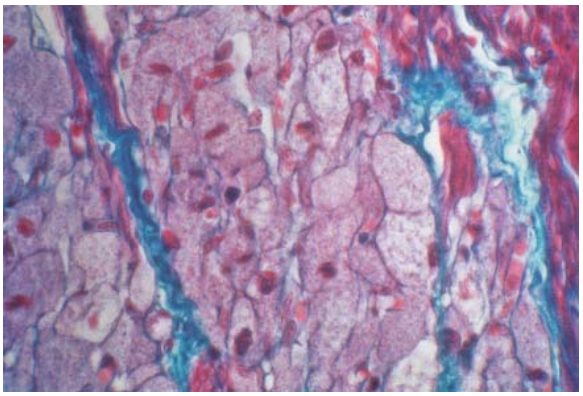

**Figure 1.** Histiocytoid cardiomyopathy. Microscopic section of myocardium showing vacuolated cells beneath the endocardium (from Gilbert Barness, Kapur, Oligny & Siebert: Potter's Pathology of the Fetus, Infant and Child © 2007 Elsevier Inc. with permission).

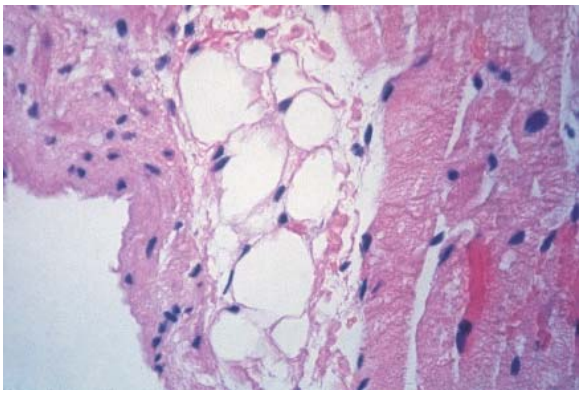

**Figure 2.** Arrhythmogenic right ventricular dysplasia. Microscopic section showing lipid deposits in the myocardium (from Gilbert Barness, Kapur, Oligny & Siebert: Potter's Pathology of the Fetus, Infant and Child © 2007 Elsevier Inc. with permission).

tachycardia, and, frequently, sudden death in the first 2 years of life (1,2,3,4). Some reports have included children up to 4 years of age (5,6). Female preponderance is approximately 4:1 (7). Most cases (90%) occur in female children under 2 years of age, leading to intractable ventricular fibrillation or cardiac arrest. The lesion resembles a hamartoma with histiocytoid or granular cell features (4). It has clearly been defined as a mitochondrial disorder of complex III (reduced coenzyme Q-cytochrome c reductase) of the respiratory chain of the cardiac mitochondria (4). It has been associated with congenital cardiac defects (4,5,7). The etiology favors either an autosomal recessive gene or an X-linked condition (8,9). Female predominance may be explained by gonadal mosaicism for an X-linked mutation. The latter seems likely because of the reported association with another rare X-linked condition, microphthalmia with linear skin defects (MLS) that is monosomic for Xp22 (8). An X-linked dominant mutation has been associated with lethality in the male. One sporadic case of the A8344G mtDNA mutation, best known for the myoclonic epilepsy, myopathy, and ragged red fibers (MERRF) phenotype, in an infant with histiocytoid cardiomyopathy and sudden death at 11 months of age has been reported (10).

Histopathological findings in patients with histiocytoid cardiomyopathy include multiple flat-to-round, smooth, yellow nodules located beneath the endocardial surface of the left ventricle, the atria, and the four cardiac valves. The nodules are composed of demarcated, large, foamy granular cells (Figure 1). Glycogen, lipid, and pigment may be seen in these cells, as well as a lymphocytic infiltrate. Immunostaining shows perimembranous immunoreactivity for muscle-specific actin, but not for the histiocytic markers, S-100 protein and CD69 (KP) (11,12,13,14,15). These cells may be abnormal Purkinje cells, but a primitive myocardial precursor cannot be excluded. Radiofrequency ablation of a conduction defect may be an effective treatment for dysrhythmias (16). Surgical intervention with prolonged survival has been reported (17).

### 3.2. Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is occasionally present in infants. Ventricular tachycardia, left bundle branch block, and right ventricular dilatation characterize the clinical features (18). A recent infection frequently precedes the onset of symptoms (19). The principal histologic finding in a biopsy of the right ventricle of an affected patient is fatty infiltration (Figure 2), with or without interstitial fibrosis of the myocardium. Cardiac enlargement is mostly localized to the right ventricle, although similar abnormalities may be present on the left side of the heart (20). There are more than 200 reported cases, with a mean age of presentation of 30 years and a 2:1 to 3:1 male preponderance. At least 30% of cases are familial (21,22). Two patterns of inheritance have been described in ARVC: an autosomal dominant form, which is most common, and an autosomal recessive form called Naxos disease, in which ARVC is part of a cardiocutaneous syndrome including hyperkeratosis of the palms and soles and woolly hair (23). Disease loci for the autosomal dominant disorder have been mapped to chromosomes 14q23-q24 (ARVC1) (24), 1q42-q43 (ARVC2) (25), 14q12-q22 (ARVC3) (26), 2q32 (ARVC4) (27), 3p25 (ARVC5) (28,29), 10p12-p14 (ARVC6) (30), 10q22, 6p24 (ARVC8) (22,31), and 12p11 (ARVC9) (32). Desmoplakin was the first disease-causing gene identified in autosomal dominant ARVC; the affected family had a missense mutation linked to 6p24 (ARVC8) (22). Desmoplakin is a key component of desmosomes and adherens junctions that is important for maintaining the tight adhesion of many cell types, including those in the heart and skin. When these junctions are disrupted, cell death and fibrofatty replacement occur. Five established disease-causing genes in ARVC encoding desmosomal proteins — plakoglobin, desmoplakin, plakophilin-2, desmoglein, and desmocollin in autosomal dominant disease and plakoglobin and desmoplakin in Naxos disease — support a new model for the pathogenesis of ARVC (33). Impaired desmosome function when subjected to mechanical stress causes myocyte detachment and cell death. The myocardial injury

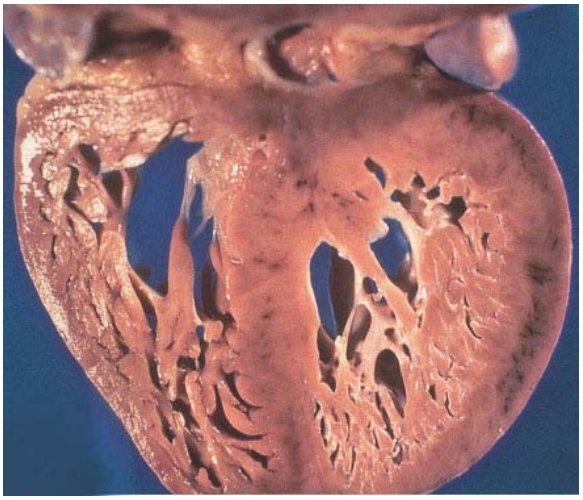

**Figure 3.** Noncompaction of the left ventricle with coarse trabeculation (from Gilbert Barness, Kapur, Oligny & Siebert: Potter's Pathology of the Fetus, Infant and Child © 2007 Elsevier Inc. with permission).

may be accompanied by inflammation as the initial phase of the repair process, which ultimately results in fibrofatty replacement of damaged myocytes.

In a study of 60 cases with sudden death in young northern Italians, at least 20% had histological evidence of right ventricular dysplasia at autopsy. Although 10% of such patients are asymptomatic (34), they may present with palpitations, syncope, congestive heart failure, or even sudden death, and these episodes are commonly precipitated by exertion. The classic electrocardiographic finding is ventricular tachycardia, often with left bundle branch block. The optimal strategies for preventing sudden cardiac death and the indications for implantable cardioverter-defibrillator therapy in patients with ARVC are not well defined (35).

### 3.3. Isolated noncompaction of the left ventricle myocardium

Isolated noncompaction of the left ventricle myocardium (LVNC) (persistence of spongy myocardium) is a rare form of congenital cardiomyopathy in which the left ventricular wall fails to become flattened and smoother than it normally would during the first 2 months of embryonic development (Figure 3). This developmental arrest results in decreased cardiac output with subsequent left ventricular hypertrophy. Persistence of noncompacted myocardium may be associated with structural heart defects or may be isolated (36). In adult patients the diagnosis is often limited to patients without associated cardiac defects ("isolated" LVNC) (37,38). However in children, concomitant heart defects have been described in 14% of patients (39). Associated conditions include coronary artery anomalies (anomalous origin of the left main coronary artery from the pulmonary trunk and coronary ventricular fistulae) and conotruncal anomalies (absent pulmonary valve, pulmonary atresia, tricuspid atresia and transposition of the great arteries) (40). Burke *et al* (41) reported a high rate of coexisting cardiac anomalies (8 of 14 cases), including ventricular septal defect, anomalous venous pulmonary veins, coronary ostial stenosis, histiocytoid cardiomyopathy, polyvalvar dysplasia and pulmonary stenosis. Syndromes associated with noncompaction of the ventricles include Barth syndrome (42,43,44) which may be genetically related, congenital adrenal hyperplasia (41), DiGeorge sequence (39), myopathic changes with inclusions in skeletal muscle fibers (39), Melnick-Needles syndrome (45), Cornelia De Lange syndrome (46) and Pierre Robin syndrome (46). The genetic basis for isolated LVNC and LVNC with congenital heart disease is unknown, although there have been reports of mutations in the G4.5 and alpha-dystrobrevin genes in infants (47), with possible X-linked inheritance (46,47,48) and an autosomal dominant inheritance in the adult form (48). In clinical series of children, there is generally no sex predilection and age at presentation ranged from 1 day to 17 years (39,49). In the series of Burke *et al* (41) with 13 autopsy cases (and 1 explanted heart), the neonatal deaths were exclusively girls, suggesting that LVNC in girls presenting soon after birth may be an especially lethal form of the disease. There was no increase in the frequency of associated anomalies in the female patients in their study to explain the earlier age at death.

The aberrant left ventricular trabeculae predispose to cardiac conduction abnormalities and potentially fatal cardiac arrhythmias. The interstices within the trabeculated left ventricle predispose to thrombus formation with secondary systemic embolic events. Fibroelastosis of the adjacent ventricular endothelium is a secondary phenomenon, resulting from an abnormal blood flow pattern in the left ventricular chamber (50). The clinical course of LVNC is variable but is characterized by gradually depressed left ventricular function, with heart failure developing in more than 50% of patients within 4 years, ventricular arrhythmias, and thromboembolism (41). There is no specific therapy for LVNC. Medical management varies with the clinical manifestations, left ventricular ejection fraction, and the presence or absence of arrhythmias.

### 3.4. Long QT syndrome

Long QT syndrome (LQTS) is a heterogeneous group of disorders characterized by prolongation of the corrected QT interval (Qtc) on the surface electrocardiogram, seizures, syncope and sudden death. Mortality is presumably due to cerebral hypoperfusion during malignant ventricular tachycardia, known as "torsades de pointes". The defect lies in abnormal myocardial repolarization, creating a vulnerable refractory period at risk for ventricular tachycardia. Patients are usually detected during the evaluation for syncope or seizures, though for many the initial presentation is aborted sudden death. The several genetic defects are listed in Table 1. Multiple different types of congenital LQTS have been identified (51,52). Distinct genetic types have been designated LQT1 through LQT10, however LQT1, LQT2 and LQT3 account for over 90% of cases of congenital LQTS (53,54). A single mutation (heterozygous state) in any one of the LQT1 through LQT7 genes results in an

**Table 1**. Molecular genetics of long QT syndrome[1]

| LQTS Type (Year Discovered) | Mutant Gene (Alternate Name) | Chromosomal Locus | Ion Currents Affected By the Mutant Gene |
|---|---|---|---|
| LQT1 (1991) | KCNQ1 (KVLQT1) | 11p15.5 | Decreased slowly activating delayed rectifier K+ repolarization current ($I_{ks}$) |
| LQT2 (1994) | HERG | 7q35-36 | Decreased rapidly activating delayed rectifier K+ repolarization current ($I_{kr}$) |
| LQT3 (1994) | SCN5A | 3p21-24 | Increased Na+ current ($I_{Na}$) due to late reopening of the sodium channel |
| LQT4 (1995) | Ankyrin B | 4q25-27 | Possibly increased late Na+ current ($I_{Na}$) |
| LQT5 (1997) | KCNE1 (minK) | 21q22.1-22.2 | Decreased slowly activating K+ repolarization current ($I_{ks}$) |
| LQT6 (1999) | KCNE2 (MRP1) | 21q22.1-22.2 | Decreased rapidly activating K+ repolarization current ($I_{kr}$) |
| LQT7 (2001) | KCNJ2 | 17q23 | Decreased inwardly rectifying K+ current ($I_{kr2.1}$) |
| LQT8 (2001) | CACNA1C | 12p13.3 | Increased L-type calcium current |
| LQT9(2006) | CAV3 | 3p25 | Persistent late sodium current |

[1] Adapted from Moss AJ. Long QT Syndrome. *JAMA* 289, 2041-2044 (2003)

autosomal dominant form of LQTS, the Roman Ward syndrome (55,56,57,57,59). The presence of 2 mutations (homozygous state) in either the LQT1 or LQT5 gene results in a severe autosomal recessive form of LQTS with associated deafness; the Jervell and Lange-Nielsen syndrome (55,58,60). Mutations in the LQT7 are responsible for Andersen syndrome (hypo-kalemia periodic paralysis), a rare neurologic disorder characterized by periodic paralysis, skeletal developmental abnormalities and QT prolongation with ventricular arrhythmias that are exacerbated by hypokalemia (61). Mutations in the LQT8 result in Timothy syndrome, a very rare multisystem disorder with major phenotypic abnormalities including syndactyly, dysmorphic features, cognitive deficits, autism, immune deficiency, congenital heart disease, and arrhythmias (62). Severe QT prolongation was seen in all affected individuals (62). For LQT9 and LQT10 there are only preliminary descriptions (63,64) and at this time should be regarded as putative forms of long QT syndrome (65).

### 3.5. Brugada syndrome

Brugada syndrome may present with sudden cardiac death as the first and only clinical event. It was introduced as a clinical entity in 1992 (66). Cases in children ranging from infancy to 16 years have been reported (66,67) although arrhythmic events mostly occur in adulthood (68,69). Arrhythmic events in children with Brugada syndrome are uncommon, but fever has been reported as a prominent trigger of events (67). Brugada syndrome has a characteristic electrocardiographic (ECG) pattern with right bundle branch block (RBBB) and persistent ST segment elevation in leads V1-V3 (66,70,71,72). The Brugada syndrome has an autosomal dominant inheritance with variable expression. Several dozen mutations in SCN5A, the gene that encodes the alpha subunit of the cardiac sodium channel gene, have been found (68,73,74,75,76,77). The mutations have been shown to result in either (1) failure of the sodium channel to express; (2) reduced current due to a shift in the voltage and time dependence of sodium channel current (I Na) activation, inactivation or reactivation; or (3) reduced contribution of I-Na during the early phases of the action potential resulting from accelerated inactivation of the sodium channel (78). The premature inactivation of the channel was observed at physiological temperatures, but not at room temperature (79), hence the suggestion that the syndrome may be unmasked, and that patients with the Brugada syndrome may be at an increased risk, during a febrile state (79). The gene locus is located on chromosome 3p21-24. Another locus on chromosome 3, close to but distinct from SCN5A, has also been linked to the syndrome (80). Brugada syndrome is not usually associated with structural heart disease and the diagnosis is based on clinical criteria (81). Implantable cardioverter-defibrillator is the only treatment with proven efficacy (82).

### 3.6. Congenital short QT syndrome

Congenital short QT syndrome is a new familial primary electrical disease of the heart which is characterized by abnormally short QT interval and paroxysmal atrial and ventricular tachyarrhythmias, including sudden cardiac death (83). To date only a few families have been identified (84,85). Genetic mutations in KCNH2 in familial forms (86) and KCNQ1 in sporadic cases (87) have been identified. A missense mutation (C to G substitution at nucleotide 1764) which resulted in the amino acid change (N588K) in KCNH2 has been identified by Hong *et al* (88) in three families with the disease, and they concluded that codon 588 is a hotspot for this familial form of short QT syndrome. Biophysical analysis indicated that the mutation was creating a "gain of function" in IKr current, causing a shortening of the action potential. This current is largely responsible for repolarization and thus the QT interval duration (89). The mutation increases IKr, leading to a shortening of action potential duration and refractoriness, creating the substrate for reentrant arrhythmias (86,88). The gene map locus is 7q35-q36. In the reported families with short-QT syndrome the median age at diagnosis was 30 years (85). Sudden death in the presence of short QT interval is reported in several generations, in both male and female subjects, which suggests an autosomal dominant mode of inheritance (90). Cardiac arrest may be the first clinical presentation and has been reported in patients from 3 months to 62 years of age (85,90). From the clinical point of view this syndrome has a broad clinical phenotype and a wide range of symptoms, even in families with the same mutation (88). The optimal therapy for short QT syndrome has not been established (84).

### 3.7. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT), also known as familial catecholaminergic polymorphic ventricular tachycardia,

occurs in the absence of structural heart disease or known associated syndromes (91-99). It is an autosomal dominant, inherited disease with a relatively early onset and a mortality rate of approximately 30% by the age of 30 years (97). It is characterized by episodes of syncope, seizures, or sudden death in response to physiological or emotional stress (98). The disorder typically presents in childhood or adolescence (91,92,94). Mutations in the cardiac ryanodine receptor gene (RyR2), which encodes a cardiac sarcoplasmic reticulum (SR) Ca(2+) release channel (94,96,97,100), mapped to chromosome 1q42-q43 (95), have been identified in some families with the disease (94,95,96,97). A second genetic form with autosomal recessive inheritance, involves the calsequestrin 2 gene (CASQ2), mapped to chromosome 1p13-21 (98,101,102). Polymorphic VT may also present in patients with no significant structural heart disease and no family history (103). Some, but not all of these patients have de novo mutations similar to mutations observed in patients with familial disease (94,104,105). Beta-blockers are the cornerstone of therapy, but some patients do not have a complete response to this therapy and receive an implantable cardioverter-defibrillator (104).

## 4.SUMMARY

In some arrthyhmogenic diseases causing sudden cardiac death, the autopsy demonatrates structurally normal hearts and no obvious cause of death. The molecular basis of this group of disorders is increasingly coming to light, with some disorders well described at the molecular level. For the pathologist involved in such cases, it is prudent to retain frozen myocardial samples, and when possible, obtain blood for DNA extraction, as well as saving formalin fixed paraffin embedded tissues for molecular studies.

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**Key Words:** Conduction Defects, Child, Cardiomyopathy, Arrhythmia, Congenital, Review

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