ECG Patterns and Genotypes in Pediatric Patients with Channelopathies - 7-year Experience in Slovakia

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Abstract. *Primary genetic arrhythmias or channelopathies are associated with mutations of genes encoding proteins creating or interacting with the specialized ion channels in the myocardial cell membranes. The resulting increased or decreased ion channel function forms the arrhythmogenic substrate predisposing the patient with structurally normal heart to sudden cardiac death on the basis of ventricular tachycardia or fibrillation. The study focuses the clinical and ECG presentation and management of children with channelopathies in Slovakia. 18 children with suspected primary genetic arrhythmia were admitted to the Children's Cardiac Center Bratislava in the years 2007 – 2013. Results: in 10 patients the underlying channelopathy has been genetically proven: syndrome of long QT interval in 7 and catecholaminergic polymorphic ventricular tachycardia in 3 patients. The remaining patients are in the process of genetic testing, 4 of them with obvious symptoms of channelopathy. Sixteen children are treated with betablockers, 5 in combination with mexiletine or flecainide, 7 patients received implantable cardiac defibrillator and one underwent left cardiac sympathetic denervation. None of the treated patients died. Conclusion: Early diagnosis of channelopathies allows for adequate treatment and lifestyle modification. Genetic testing is important both for the optimal management of the patient and the family.*

Keywords: channelopathy, genetic testing, children

1. Introduction

Primary genetic arrhythmias or channelopathies are associated with mutations of genes encoding proteins creating or interacting with the specialized ion channels in the myocardial cell membranes. The resulting changes in the ion channel function form the arrhythmogenic substrate predisposing the patient with structurally normal heart to sudden cardiac death (SCD) on the basis of ventricular tachycardia (VT) or fibrillation [1, 2]. Channelopathies are a heterogenous group of diseases with many different causative genes. Three most commonly occurring types are long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS).

LQTS is characterized by QT prolongation and T wave abnormalities, specific type of arrhythmia - torsades de pointes (TdP), and predisposition for syncope, seizures and sudden cardiac death. TdP is a specific type of ventricular tachycardia (Fig. 1), often self-limiting with transient syncope, but it can also degenerate into ventricular fibrillation and cardiac arrest [3, 4]. LQTS represents a leading cause of autopsy-negative sudden death in the young [5]. Three main genes responsible for the 3 most common types of LQTS (gene KCNQ1 in LQT1, KCNH2 in LQT2 and SCN5A in LQT3), account for approximately 75% of clinically definite LQTS, minor genes contribute an additional 5% and about 20% of LQTS remain genetically elusive [2, 4, 6]. Diagnosis of LQTS is made when modified Schwartz risk score is more than 3.5 (Fig. 2) and/or pathogenic mutation of one of the LQTS genes is found or corrected QT interval of more than 500 ms is reproducibly measured on the native ECG. The

estimated yield of the genetic testing in LQTS is about 60%. Treatment options for LQTS patients include life-style modification with avoidance of specific arrhythmia triggers and QT interval prolonging drugs, beta-blockers (BB), mexiletin in LQT3, left sympathetic cervical denervation (LSCD) and implantable cardiac defibrillator (ICD) [2].

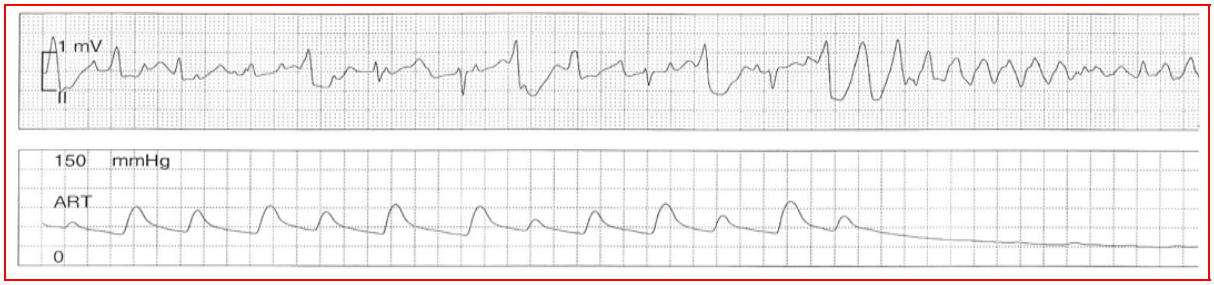

Fig. 1. Episode of torsade de pointes (in neonate with LQT3) on ECG monitor (lead II) - top part of the figure, with invasive arterial blood pressure (ABP) measurement - the bottom of the figure. Note the sudden fall of ABP to zero with the beginning of TdP and ventricular premature beats before the TdP starts.

CPVT is characterized by normal resting ECG and adrenergic-mediated VT: monomorphic premature ventricular beats (PVB) progressing to specific bidirectional and polymorphic PVB and VT with physical activity or emotional stress. Genes responsible for this disease are gene for ryanodine receptor RYR2 (60%) and calsequestrin CASQ2 (5%). The estimated yield of the genetic testing is around 40%. Treatment options include life-style modification with avoidance of physical activity, beta-blockers, ICD, LSCD, verapamil and flecainide [2].

Our study focuses the clinical and ECG presentation and management of children with channelopathies in Slovakia.

		Points
ECG findings*		
A.	QT_c†	
	≥480 msec$^{1/2}$	3
	460-470 msec$^{1/2}$	2
	450 msec$^{1/2}$ (in males)	1
B.	Torsade de pointes‡	2
C.	T-Wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age§	0.5
Clinical history		
A.	Syncope‡	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history‖		
A.	Family members with definite LQTS#	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

LQTS, long QT syndrome.
*In the absence of medications or disorders known to affect these electrocardiographic features.
†QT_c calculated by Bazett's formula, where $QT_c = QT/\sqrt{RR}$.
‡Mutually exclusive.
§Resting heart rate below the second percentile for age.[25]
‖The same family member cannot be counted in A and B.
#Definite LQTS is defined by an LQTS score ≥4.
Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.

Fig.2. Modified Schwartz diagnostic criteria in LQTS

2. Subject and Methods

Eighteen children aged from neonatal to 18 years with suspected primary genetic arrhythmia were admitted to Children's Cardiac Center Bratislava in the years 2007 - 2013. Twelve patients (pts.) were symptomatic, in 8 we assumed LQTS and in 4 CPVT. 6 pts. were asymptomatic with ECG features or family history of primary genetic arrhythmia, LQTS supposed in 5 and BrS in one. Characteristics of the patients are summarized in Table 1. In 13 patients with suspected LQTS, QT interval was measured and corrected for heart rate using Bazzet's formula and risk score was measured according to modified Schwartz diagnostic criteria (Fig. 3). In 4 patients with suspected CPVT, exercise testing and 24 hours ECG Holter monitoring was made to document specific arrhythmias during exercise or emotional stress. One patient had family history of Brugada syndrome with no obvious ECG pattern and parents refused any other diagnostic testing. Genetic testing was made in the diagnostic genetic center GeneDx, US, from the sample of the isolated DNA. DNA isolation was made in a genetic laboratory in Bratislava, Slovakia. Results of the genetic testing were classified

into 4 categories: disease-causing mutation, mutation likely disease-causing, variant of unknown significance or negative testing with no mutation.

3. Results

Genetic testing has been done in 15 patients (LQTS was supposed in 11 pts., 8 of them symptomatic, and CPVT in 4, all symptomatic), with 10 results until now: LQTS was diagnosed in 7 pts.: KCNQ1 gene mutation in 3, KCNH2 in 2 and SCN5A in 4 (2 children had more than one mutation), and CPVT in 3 pts.: all three RYR2 mutations. Mutations were diagnosed as disease-causing in 5 of 7 LQTS patients and as variant of unknown significance (VUS) in 2: one in a girl whose mother was resuscitated from SCD and one in the 15-years old student athlete resuscitated from SCD, in whom a year later mutation was re-classified as very likely disease-causing. From 7 LQTS patients 4 were symptomatic: 2 were resuscitated from SCD, 2-years old girl had hundreds of TdP daily with frequent loss of consciousness and last patient had recurrent syncope. In the asymptomatic patients 2 infants had prolonged QTI found on ECG made because of sinus bradycardia and one 2-years old girl had ECG made because her mother was resuscitated from SCD. 3 CPVT patients had RYR2 mutations, twins with frequent syncope and seizures and 9-years old boy resuscitated from SCD, diagnosed and treated as epilepsy for 3 years. Genetic analysis in the remaining 5 pts. haven't been finished yet, 3 have obvious symptoms of channelopathy. 3 pts. haven't been tested yet: 1 with supposed BrS, girl resuscitated from SCD with supposed LQTS and 14 years old girl with suspected LQTS who died before therapy was started and genetic testing realized. Sixteen children are treated with betablockers, 2 of them (with SCN5A gene mutation) in combination with mexiletine and 3 (CPVT) in combination with flecainide, 7 patients (5 LQTS and 2 CPVT) received ICD, 5 pts. after resuscitated SCD, 2 with recurrent syncope on BB therapy, and 2-years old girl with LQT3 with hundreds of TdP daily underwent left cardiac sympathetic denervation. None of the treated patient died, one patient with CPVT has neurologic sequelae after cardiopulmonary resuscitation. Appropriate shock was delivered in 4, inappropriate in 3 of 7 patients with ICD. Patient characteristics are summarized in Table 1.

Table 1. Characteristics of the patients: age at presentation/diagnosis, symptoms, genetic results, treatment

Pts	Age [years]	Symptoms	Susp. dg.	Gene mutation, genetic diagnosis	Treatment
1. ZP	0	Resusc.SCD, frequent TdP	LQTS	SCN5A – LQT3	ICD + BB + mexiletin
2. MN	0,1	Asympt., bradycardia	LQTS	KCNQ1 – LQT1	BB
3. KB	1	Asympt., bradycardia	LQTS	KCNQ1 + VUS in SCN5A - LQT1 (+LQT3)	BB
4. TP	2	Syncopes, frequent TdP	LQTS	SCN5A – LQT3	ICD + BB + mexiletin
5. PM	2	Asympt., near SCD in mother	LQTS	SCN5A VUS (LQT3)	BB
6. LB	9	Syncopes, disiness	LQTS	KCNQ + KCNH2 – LQT1 + LQT2	BB
7. LF	9	Resuscitated SCD	LQTS	Not finished	ICD + BB
8. JB	9	Syncopes	LQTS	Not finished	BB
9. PJ	10	Asympt., BrS in the father	BrS	Not made	No therapy
10. MU	11	Resuscitated SCD	CPVT	RYR1 – CPVT	ICD + BB
11. MD	11	Asympt., accidental finding	LQTS	Not finished	BB
12. AD1	13	Syncopes with seizures	CPVT	RYR2 – CPVT	ICD + BB + flecainide
13. AD2	13	Syncopes with seizures	CPVT	RYR2 – CPVT	BB + flecainide
14. PB	14	Asympt., accidental finding	LQTS	Not finished	BB
15. LO	14	Palpitations, chest pain	CPVT	Not finished	BB + flecainide
16. VM	15	Syncopes, SCD	LQTS	Not made	Exitus
17. MJ	18	Resuscitated SCD	LQTS	KCNH2 – LQT2	ICD + BB
18. VS		Resuscitated SCD	LQTS	Not made	ICD + BB

4. Discussion and conclusion

Primary genetic arrhythmias are uncommon diseases presenting with syncopes, seizures or SCD. These patients are not infrequently misdiagnosed and treated as epilepsy so that correct diagnosis and treatment could be delayed with the risk of life-threatening arrhythmias (9-years old boy treated as epilepsy, CPVT diagnosed after resuscitation from SCD, neurologic sequelae). Despite the fact that life-threatening arrhythmias in LQTS occur under specific circumstances in a gene-specific manner (exercise or emotional stress in LQT1, sudden noise in LQT2 and sleep in LQT3) [7], we've observed in one patient phenotype-genotype mismatch with clinical and ECG features suggesting LQT1 (exercise or emotional stress triggered TdP with their complete disappearance during sleep, delayed onset peaked T waves) and genetic result and reaction to treatment (mexiletin proved as the only effective treatment) corresponding with LQT3. In our experience in this small series of patients, genetic testing in some cases revealed dissociation of the genetic finding and the phenotypic clinical presentation. This observation reflects the continously evolving knowledge about the relation of specific mutations to clinical presentation (mutation evaluated as the variant of uknown significance in a patient resuscitated from SCD, 1 year later re-evaluated as very likely disease-causing mutation). We conclude that both the clinical presentation and genetic testing must be considered in the diagnostic and therapeutic process. Early diagnosis of channelopathies allows for adequate treatment, lifestyle modification and avoidance of specific triggers of arrhythmic events. Genetic testing is important both for the optimal management of the patient and of the family members.

References

[1] Marban E: Cardiac channelopathies, *Nature* 2002; 415(6868): 213-218.

[2] Priori SG, Wilde AA, Horie M et al: HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, *Heart Rhythm* 2013, 12: 1932-1963.

[3] Ackerman MJ, Khositseth A, Tester DJ et al: Congenital long QT syndrome in electrical diseases of the heart; genetics, mechanisms, treatment, prevention. New York: Springer Publishing, 2008, pp. 462–482.

[4] PJ Schwartz, MJ Ackerman, AL George, AAM Wilde: Impact of genetics on the clinical management of channelopathies, *Journal of American College of Cardiology* 2013; 62: 169-180.

[5] Tester DJ, Ackerman MJ: Postmortem long QT syndrome genetic testing for sudden unexplained death in the young, *Journal of American College of Cardiology* 2007; 49: 240-246.

[6] Ackerman MJ, Priori SG, Willems S, et al.: HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies. This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace* 2011;13:1077–1109.

[7] Schwartz PJ, Priori SG, Spazzolini C, et al.: Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; 103: 89-95.