

**ASSOCIATION OF A WOLFF-PAKINSON-WHITE PATTERN ALONGSIDE A
LONG QT PATTERN ON THE SAME ELECTROCARDIOGRAM RECORD.**

Keywords: Accessory pathway; Arrhythmias; Atrioventricular nodal reentrant tachycardia; Conduction system; QT prolongation; Wolff-Parkinson-White syndrome.

ABSTRACT

Background

The Wolff-Parkinson-White's syndrome (WPWS is a congenital cardiac alteration (PRKAG2. Gene map locus 7q36) with a premature depolarization of the ventricles (pre-excitation of the ventricles across of an anomalous AV conduction, in this case, across of Kent's bundle).

The Long QT's syndrome (LQTS) consists of an abnormal prolongation of the QT-interval in the ECG. It has a special capacity to predispose to the appearance of malignant cardiac arrhythmias, especially, polymorphic ventricular tachycardia, ventricular fibrillation and torsade of pointes.

If they already have little incidence separately, when they are united in an electrocardiogram, this incidence should be very much minor. In fact, we have not seen any publication about mentioned association in the current medical literature.

Aim: Our aim has been to reveal the existence of an association of a WPWS alongside a LQTS in a same person. **Methods:** We have studied 17 members of three families (10 in Family 1, 5 in Family 2 and 2 in Family 3). All patients were studied with ECG's test as fundamental test. They were also studied with EMMA genetical testing. **Results:** All affected members of the three families had a ventricular pre-excitation besides of others cardiac rhythm disturbances, concretely, Long QT's Syndrome (LQTS). **Conclusion:** By means of the following exposition, we show the existence of electrocardiographic patterns with a WPW's alongside a LQTS record.

INTRODUCTION

Both cardiological entities were described since long time ago, but independently one of other one. To do a detailed study of each one of them would be to write on something already well-known. Therefore, only we will do a shallow description of the same ones.

The Wolff-Parkinson-White syndrome

The WPW's syndrome was described by John Parkinson, Paul Dudley White y Louis Wolff, 79 years ago **(1, 2)**. It is a congenital syndrome with a premature ventricular depolarization (ventricular pre-excitation across an accessory route). Its fundamental characteristics in ECG are: short PR-interval. Delta-wave. A wide QRS-complex (greater than 120 ms) and, sometimes, alterations in ventricular repolarization. It is, then, a syndrome of pre-excitation of the cardiac ventricles due to presence of an accessory route known as Kent's bundle. This pathway has an abnormal electrical transmission between the cardiac auricle and the ventricle **(3, 4)**. Its incidence ranges between 0, 1 % and 3 % of the general population.

Notwithstanding that, the immense majority of individuals with WPW's syndrome remain asymptomatic along all your life; there is a risk of sudden cardiac death associated with this syndrome. This event is slightly frequent (less than 0,6 %), and this one is produced by the appearance of serious tachyarritmias that this anomalous route is capable of producing (in some cases, the presence of this anomalous route can unleash ventricular fibrillation, one of the principal reasons of cardiac sudden death) **(5,6,7,8)**. For its diagnosis, a good interrogation should be

present in search of syncope events or throbs (sudden perception of the own cardiac beating, normally irregular) non-explicable, that can owe to previous episodes of tachycardia related to the anomalous electrical route. Patients with WPW often show more than one accessory pathway, and in some patients as many as eight additional abnormal pathways can be found. This has been seen in individuals with Epstein's anomaly. The Wolff-Parkinson-White syndrome is sometimes associated with Leber's hereditary optic neuropathy (LHON), a form of mitochondrial disease. We must do a correct differential diagnosis among WPW syndrome, Lown-Ganong-Levine syndrome (LGL syndrome) and Mahaim's syndrome:

- WPW's syndrome or of authentic ventricular pre-excitation.
- LGL's syndrome or of accelerated atrio-ventricular conduction.
- Mahaim's syndrome: Like LGL but in this syndrome, the length of the PR-interval is normal (0.12-0.20 seconds). Sometimes may also appear a delta-wave.

In LGL's syndrome is manifested as a PR- interval less or equal than 0.12 second with normal QRS-complex duration and absence of delta-wave.

The WPW's syndrome has also been associated with atrial fibrillation (this is well-known). If the patient experiences episodes of atrial fibrillation, the ECG will show a polymorphic tachycardia of wide QRS-complex. This combination of atrial fibrillation and WPW is considered dangerous, by what are not indicated many of anti arrhythmic medicaments (9, 10). Generally, the delta-wave appears when there is

an anterograde electrical conduction between auricles and ventricles. But when there is a retrograde electrical conduction, the delta-wave disappears. This phenomenon is known as WPW "occult". Individuals with WPW's syndrome in whom the delta-waves disappear with increases in the heart rate are considered at lower risk for sudden cardiac death, this is due to disappearance of delta- wave: When disappear the delta-wave, the accessory pathway cannot conduct the electrical impulses at a high rate (in the anterograde direction). Hence these individuals will typically not have fast conduction down the accessory pathway during episodes of atrial fibrillation

The Long QT Syndrome.

Since your introduction in the cardiology (11, 12), the syndrome of Long QT has had multiple criteria for to be considered as such. The characterization proposed by the different authors for to consider an interval QT like long (or prolonged) are so many that, nowadays, it is practically impossible to reach some "consensus" on when it must be considered a cardiologic entity and when not. Something similar occurs with the "prevalence-incidence" of the same one on the general population. The incidence above-mentioned is very underestimated, even at present, but, every day there are more cases diagnosed and, therefore, every day the incidence is more important. The majority of authors define as Long interval QT when it reaches a major value of 440 ms (According to the methods of Bazzet, Fridericia, Framingham or others).

le, classic LQTS is considered a cardiologic disorder manifested on ECG by a prolongation of the QT interval (men > 440 ms and women > 450 ms) and to a great propensity to apparition of ventricular tachyarrhythmias (this is the classic definition).

According to all consulted texts, its current prevalence is 0.01-0.02 % **(13)** but it is not well defined yet and also is considerably underdiagnosed, though every day, this one this incidence growing progressively due to a major and better detection of the problem.

METHODS

The electrocardiography interpretation was made following criteria of our Master, Professor Harbel from Germany and our own criteria. We have considered as good for study when the QT-interval had a superior length to 460 ms and when the presence of delta-wave, broad QRS-complex and repolarization disturbances were evident. Measures of different intervals were made by computerized technique (pixels) as well as by manual technique.

Method used for calculate QTc value was the Framingham's method:

$$QT \text{ seconds} + 0.134 (1 - QT \text{ seconds}).$$

The genomic study was made by Department of Biochemistry and Genetics of our institution and was used EMMA™ testing, for the detection and discovery of known and unknown mutations. (Enhanced Mismatch Mutation Analysis (EMMA™) is a mutation detection method alternative to sequencing. It combines all the

advantages of screening before sequencing strategy: High throughput, high productivity).

For statistical study was used G-Star (version 3.02) valuing the descriptive parameters only (since other types of different valuations were not necessary). The used variables were: age; sex; types of detected genes; presence of access of syncope; presence of access of tachycardia (greater than 150 bpm. and existence or not of sudden cardiac death.

RESULTS (See Figure 1, 2 and Table I)

- Percentage of women: 58.82 % (10/17).
- Average of age: 27- years old.
- Percentage of genes:

HERG/ PRKAG2= 58.82 %. (LQTS2+WPWS)

KVLQT1/ PRKAG2: 41.18 %.(LQTS1+WPWS)

- Average of syncope access: 2.1176.
- Average of Tachycardia:
- ≥ 4 access= 52.94 %. ≥ 3 access= 41.18%. ≥ 2 access= 5.88 %.
- Percentage of Sudden cardiac death: (1/17) = 5.88 %

The majority of the patients were women, young (27-old years), they had an incident of tachycardia accesses equal or major that 4.

The incidence of LQT2 was discreetly top to LQT1. All patients had gene for WPWS.

All patients had also this electrocardiography pattern: A WPW image alongside Long QT-interval. In addition, all the patients had suffered; at least, one access of syncope as well as more than three accesses of tachycardia, which were nocturnal in most cases (patients were waking up from your physiological sleep).

A brief clinical introduction about patient of Figure 1

He is a 24-year-old male. From his infancy he has suffered more than 4 accesses of tachycardia and 3 documented episodes of syncope.

He was treated to two electrical shocks without result. Later it was treated to ablation by radio frequency of Kent's bundle, with positive result.

A brief electrocardiography description

There is a constant stimulation with sinusal rhythm to 66-67 bpm approximately.

The R-R-interval is irregular to 0.880-0.908 seconds. P-wave fundamentally positive on D1, D2, D3, and negative on V1, V2 and it also is regular and followed by QRS-complex (there is a migrant pacemaker). There also is a short PR-interval to a value 0.108 seconds. The electrical axis inside normal values. There are not S1Q3, S1S2Q3 or S1Q3T3 patterns. Widened QRS-complex on its base to 0.14-0.15 seconds and normal on its apex (presence of delta-wave). R-wave's progression on precordial leads is irregular. There are intense signs of ventricular

hypertrophy so much right as left (Sokolow-Lyon). T-Wave variable has an asymmetric investment on precordial lead lefts. It is evident a Long QT-interval, ranging between 0.472-and 0.542 seconds. QTc-Interval prolonged (Framingham's method): 0.488- 0.554 seconds.

Diagnosis ECG.

1. Wolff-Parkinson-White pattern. (Presence of short PR-interval, delta-wave, widened QRS-complex and alterations of ventricular repolarization)
2. Prolonged QT-interval pattern.

DISCUSSION.

Analyzing the obtained results, we observe as these patients had presented some events of syncope, tachycardia (even one sudden cardiac death) as well as also your more direct relatives. Absolutely all patients were diagnosed of Wolff-Parkinson-White's Syndrome. Nevertheless the presence in the ECG of a concomitant Long QT's Syndrome happened unnoticed.

Wolff-Parkinson-White is one of the most common causes of fast heart rate disorders in infants and children **(2)**. Normally, electrical signals in the heart go through a pathway that helps the heart beat regularly. The wiring of the heart prevents extra beats from occurring and keeps the next beat from happening too soon, however, in people with Wolff-Parkinson-White syndrome there is an extra, or accessory, pathway that may cause a very rapid heart rate (supraventricular tachycardia) **(3)**. Some people with Wolff-Parkinson-White syndrome may have just a few episodes of rapid heart rate. Others may have the rapid heart rate once or

twice a week. Sometimes there are no symptoms, and the condition is detected when a heart tests is done for another reason. A person with WPW syndrome may have:

Chest pain or chest tightness. Dizziness. Light-headedness. Fainting. Palpitations. Shortness of breath. An exam performed during a tachycardia episode will reveal a heart rate greater than 230 beats per minute and blood pressure that is normal or low. A normal heart rate is 60 - 100 beats per minute in adults, and under 150 beats per minute in neonates, infants, and small children. If the patient is currently not having tachycardia, the physical exam may be completely normal. The test called EPS may help identify the location of the extra electrical pathway. Wolff-Parkinson-White syndrome may be revealed by the following tests:

- ECG (electrocardiogram) may show an abnormality called a "delta" wave.
- Continuous ambulatory monitoring (Holter monitor).

Medication may be used to control or prevent rapid heart beating. The atrial fibrillation is the most serious arrhythmia associated with a WPW because can produce a ventricular fibrillation. In this case are contraindicated all drugs that interfere with AV conduction such as calcium channel blockers, digitalis and adenosine. If the heart rate does not return to normal with medication, we may use electrical cardioversion. The current therapy of election for Wolff-Parkinson-White syndrome is catheter ablation (**9, 10**). Open heart surgery may also provide a permanent cure for Wolff-Parkinson-White syndrome. However, surgery is usually done only if the patient must have surgery for other reasons.

The Long QT syndrome like we have already said in "Introduction" can be inherited or acquired. Patients with LQTS have a special predisposition to the ventricular tachyarrhythmia (ventricular fibrillation fundamentally) and torsade de pointes (TdP) which can cause syncope and sudden death (**13**). The inherited LQTS is the prototype of cardiac ion channelopathies (**Table II**). The study of inherited LQTS has provided great insight into cardiac arrhythmogenesis.

LQTS is caused by mutations of genes which encode for cardiac ion channels. The genes have been numbered in the order of discovery as LQT1, LQT2, etc. Twelve genes, with over 200 mutations have thus far been discovered. Most families have their own mutation, and there are no special points, although some exons have a higher number of described mutations than others. For example, the gene locus for LQT4 has been mapped to chromosome 4, but the gene itself has not yet been identified. (**See Table II**).

Using published genotype information, phenotype analysis by ECG findings, and event triggers of patients from centers around the world, it appears that about 95% of LQTS cases are caused by mutations of the potassium genes. Approximately 30% of phenotypically affected subjects have no mutation identified on genetic analysis. Patients may have mutations of genes not yet recognized. Alternatively, they may have mutations of non-coding regions of the known genes, or regulatory or modifier genes. Approximately 60% of LQTS patients have the LQT1 form.

Exercise and emotion are the triggers for over 90% of cardiac events. LQT1 occurs when a patient has a mutation of the KCNQ1 or KCNE1 genes, causing defective

IKs channels. The mean QTc in LQT1 is 0,490 seconds, with a range from 0,410 to over 0,600 seconds. LQT2 is caused by mutations of the HERG or KCNE2 genes.

Mutations of these genes cause defective IKr channels. The mean QTc in LQT2 patients is 0,480 seconds, with a range from 0.410 to about 0,600 seconds. About 17% of LQT2 patients have a normal QTc (< 0.440 seconds) on baseline ECG, and about 30% have an interval of < 0.460 seconds **(14, 15, 16, 17, 18)**. Thus, LQT2 patients are more commonly missed on baseline ECG than the other genotypes.

The finding of bifid T-waves in the inferior and lateral leads on the ECG may aid for its diagnosis. Syncope is common in the normal population, and occurs at the same frequency in LQTS patients. The details of the syncope history are usually the key to the correct diagnosis. In LQTS it is precipitous and without warning in the vast majority of cases, and the duration of the syncope is longer than the usual very brief vasovagal event.

A history of unexplained sudden death or repetitive syncope in young members of a family with similar symptoms or with some sudden cardiac death is certainly suspicious for LQTS. However, at least one-third and probably about one-half of gene carriers have never symptoms, and it is not uncommon for the family history can be negative at the time of diagnosis in a member. The characteristic ECG signs are QT interval prolongation and T wave abnormalities. The QT shows reduced penetrance and variable expression, and diagnosis may be difficult by this parameter. There is significant variability of the QTc within members of any family, between families and to a much lesser extent, between genotypes. QT interval: The

QTc ranges from about 0,410 to over 0,600 seconds. The range of values in a normal population is about 0,350 to 0,460 seconds. Consequently, there is overlap of QTc values between LQTS and normal in the 0,410 to 0,460 seconds range. Values in this range are non-diagnostic and further studies are required. QTc intervals of $\leq 0,440$ seconds (commonly used as upper 95th percentile normal value) on resting ECG are seen in about 12% of gene carriers overall and this varies by genotype. Approximately 30% of carriers have a normal to borderline QTc 0,410 - 0,460 seconds. About 60% of the normal population has a QTc of 0,410 - 0,460 seconds, so when screening patients for possible LQTS a large percentage will have QTc values which can neither make nor exclude the diagnosis of LQTS. The patients affected by the long Q-T syndrome (LQTS) are characteristically likely to present episodes of alternation of the T-wave following the same stimuli which trigger the syncopal attacks, and often these episodes of alternation precede or follow ventricular fibrillation. Since its first description in 1957, progress was made in the understanding and in the treatment of this often fatal syndrome. In spite of these recent advances there is still much confusion about the LQTS, and the uncertainty as to its pathogenesis often leads to the application of a variety of therapies and to the frequent change of drugs, the general results being poor. Moreover, there are entirely too many patients who remain undiagnosed due to the lack of knowledge of this syndrome, and eventually die. Nowadays the pathogenetic mechanisms, although not completely elucidated, are better

understood, and effective treatments are available, greatly reducing the risk of sudden death in patients properly treated.

CONCLUSIONS.

When we face an unknown picture and, therefore, there are no referential baselines, is frankly difficult to draw strict conclusions.

Is this presentation an isolated incident or not? It's evident that no, because has been manifested by 17 different patients and they are symptoms and genetic conditions common among them. We are, then, in front of a new electrocardiography pattern what has a combination of genes: WPWS and LQTS. Possibly these pattern types have not had a good diagnosis, previously. But its existence is very clear.

In the presented study, as we have already exhibited in the paragraph "Results", characteristics were: The majority of the patients were women, young (27-old years), they had an incident of tachycardia accesses equal or major that 4.

The incidence of LQT2 was discreetly top to LQT1. All patients had gene for WPWS and LQTS. All patients had this electrocardiography pattern: A WPW image alongside Long QT-interval. In addition, all the patients had suffered; at least, one access of syncope as well as more than three accesses of tachycardia, which were nocturnal in most cases (were waking up the patients from your physiological sleep).

Our research team is working now about the possible existence of other gene type that can explain this strange association. But outcomes still are not viable, because the research is in process currently.

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TABLE I

Characteristics of seventeen valued patients: Age. Sex. Upset genes. Episodes of syncope. Episodes of tachycardia / palpitations. Sudden cardiac death.

VARIABLES					
AGE	SEX	GENE	SYNC.	PALP,/TACHY	SCD
FAMILY 1					
13	Female	HERG/ PRKAG2	1	> 3	No
16	Female	HERG/ PRKAG2	1	> 4	No
23	Male	HERG/ PRKAG2	1	> 3	No
25	Male	HERG/ PRKAG2	3	> 4	No
18	Female	HERG/ PRKAG2	2	> 3	No
24	Male	HERG/ PRKAG2	3	> 4	No
54	Female	HERG/ PRKAG2	4	> 4	No
36	Male	HERG/ PRKAG2	3	> 3	No
32	Male	HERG/ PRKAG2	1	> 4	No
18	Female	HERG/ PRKAG2.	2	> 4	No
FAMILY 2					
19	Female	KVLQT1/ PRKAG2	2	> 4	No
21	Male	KVLQT1/ PRKAG2	2	> 3	No
33	Female	HERG/ PRKAG2	3	> 3	No
24	Male	KVLQT1 PRKAG2/	3	> 2	No
27	Female	KVLQT1 PRKAG2	3	> 4	Yes
FAMILY 3					
31	Female	KVLQT1/ PRKAG2	2	> 4	No
45	Female	KVLQT1/ PRKAG2	2	> 3	No

All patients had this electrocardiography pattern: A WPW image alongside Long QT-interval.

TABLE II

General characteristics on the responsible genes for WPWS and LQTS.

Type	OMIM	Mutation	Notes
LQT1	192500	alpha subunit of the slow delayed rectifier potassium channel (KvLQT1 or KCNQ1)	The current through the heteromeric channel (KvLQT1 + minK) is known as I_{Ks} . These mutations often cause LQT by reducing the amount of repolarizing current. This repolarizing current is required to terminate the action potential, leading to an increase in the action potential duration (APD). These mutations tend to be the most common yet least severe.
LQT2	152427	alpha subunit of the rapid delayed rectifier potassium channel (HERG + MiRP1)	Current through this channel is known as I_{Kr} . This phenotype is also probably caused by a reduction in repolarizing current.
LQT3	603830	alpha subunit of the sodium channel (SCN5A)	Current through this channel is commonly referred to as I_{Na} . Depolarizing current through the channel late in the action potential is thought to prolong APD. The late current is due to the failure of the channel to remain inactivated. Consequently, it can enter a bursting mode, during which significant current enters abruptly when it should not. These mutations are more lethal but less common.
LQT4	600919	anchor protein Ankyrin B	LQT4 is very rare. Ankyrin B anchors the ion channels in the cell.
LQT5	176261	beta subunit MinK (or KCNE1) which coassembles with KvLQT1	
LQT6	603796	beta subunit MiRP1 (or KCNE2) which coassembles with HERG	
LQT7	170390	potassium channel KCNJ2 (or $K_{v}2.1$)	The current through this channel and KCNJ12 ($K_{v}2.2$) is called I_{K1} . LQT7 leads to Andersen-Tawil syndrome.
LQT8	601005	alpha subunit of the calcium channel Cav1.2 encoded by the gene CACNA1c.	Leads to Timothy's syndrome.
LQT9	611818	Caveolin 3	
LQT10	611819	SCN4B	
LQT11	611820	AKAP9	
LQT12	601017	SNTA1	

FIGURE 1

Electrocardiogram's record (12 leads). We can see the presence of WPWS alongside LQTS.

**FIGURE 2**

Enlarged detail of the entire cardiac cycle on D2. Has been specified so much the delta wave presence as length of QT-interval. It is also illustrated an image of EPS.

