The Romano-Ward syndrome: 1964-2014: 50 years of progress

Abstract:


This year marks the 50th publication of a syndrome in the Journal of the Irish Medical Association in 1964. The syndrome was described by Irish paediatrician Professor Conor Ward entitled A new familial Cardiac Syndrome in Children. The condition soon became known by the eponym Romano-Ward Syndrome and is now recognised as the congenital Long QT Syndrome. Here we review the major developments in the field over the past fifty years, with special mention of the important contributions made by Irish researchers.

Two pivotal publications on LQTS appeared in 1985. Schwartz formulated diagnostic criteria, particularly useful in distinction between acquired and congenital LQTS and again commented on the unanswered questions regarding risk. In the same year, in one of his first publications on the subject (now totalling >160), Peter Schwartz reported 6 new cases of a different form of congenital LQTS, which he called Romano-Ward Syndrome. Here we review the major developments in the field over the past fifty years, with special mention of the important contributions made by Irish researchers.

Romano-Ward Syndrome

The Romano-Ward Syndrome is a condition characterised by a prolonged QT interval and a familial incidence. The now pathognomonic trio of symptoms and signs of the Long QT Syndrome (LQTS) as described by Professor Ward in his 1964 Journal of the Irish Medical Association case series publication. A 6-year-old girl, suffering from repeated syncope, had been referred for cardiology review by her tenacious GP who thus far, had unsuccessfully consulted widely on this troublesome and novel case. The child was admitted to hospital and her symptoms recreated by running her around the ward. She collapsed, pulseless and unresponsive. With remarkable foresight the electrocardiographic changes were punctually described marked QT prolongation at baseline and bizarre ventricular extrasystoles degenerating into ventricular fibrillation of an abnormal configuration. We now know this to represent Torsades de pointes.

Fortuitously, the IMJ article was picked up by The Lancet and published as an Annotation in their July issue 1964. It noted that the first time this condition had been described and they recommended that an ECG be considered prior to any further anaesthetic procedures. Subsequently, these children were referred to Professor Arthur Moss at the University of Pennsylvania who performed a left stellate ganglion block, of which the author, it was correctly concluded that this new disorder was an abnormality of repolarisation – 'as evidenced by the normal interval between the first and second heart sounds, the abnormality is confined to the recovery phase in which the heart prepares for the next contraction'. Furthermore, it was suggested that undue sensitivity of the myocardium to sympathetic stimulation may underlie the condition, as all the children were very small in stature, with the dilated pupils of the child. In terms of heritability, it was noted that the child's brother was also affected. Moreover, the mother's ECG was described. As did their relatives, she had a normal ECG however, the ECG showed QT prolongation. It was concluded from these observations that this cardiac syndrome had an autosomal dominant inheritance pattern.

Meanwhile, in the North of Ireland, at Queen's University Belfast, Professor (now Sir) Peter Froggatt was collaborating with researchers in Oxford and Detroit to perform ECGs on congenitally deaf people throughout Ireland and Australia. The first publication in 1964 and they succeeded in assessing the QT interval of 1460 patients. From these, nine new cases of JLN were identified, four of them from Ireland. In order to define the normal QT interval in children, in their population, they conducted ECGs in a control group of 369 Belfast school children and measured the distribution of the QT interval. The group also produced a regression equation to normalise QT for age, sex and heart rate. This equation was essentially a paediatric QT correction formula. In their discussion, the authors touch on some of the issues that remain pertinent in the Long QT community today. They note that, even within families, penetrance (as measured by the QT interval) seems to be varied and not necessarily linked to mortality. Approximately ten years later in the era of genetic testing, while risk stratification in LQTS is somewhat more accurate, the same questions in regard to variable presentation of LQTS genotypes remain.

A decade later, in one of his first publications on the subject (now totalling >160), Peter Schwartz reported 6 new cases of long QT in both deaf and normal hearing children. This brought the total reported cases to 203. This particular publication is notable for several reasons. First, it described the successful therapeutic use of verapamil, as the first report on the efficacy of verapamil in the treatment of LQTS appeared in the Lancet. This was followed by a report in 1958, they also performed a left stellate ganglion block, which successfully shortened the QT interval and rendered the patient syncope-free. Second, this paper also introduced the key concept of the importance of T wave morphology in addition to the QT interval, made the distinction between acquired and congenital LQTS and again commented on the unanswered questions regarding risk stratification and penetrance. Additionally, the umbrella term Long QT Syndrome, encompassing both Romano-Ward and Jervell Lange-Nielsen, first appeared in this article.

Two pivotal publications on LQTS appeared in 1985. Schwartz formulated diagnostic criteria, particularly useful in borderline cases and the first report from the International Long QT registry was published in Circulation. The former brought forth the importance of T wave morphology into the diagnostic criteria. They identified 21 risk factors for sudden death namely congenital deafness, history of syncope, female gender and documented Torsade de pointes or ventricular fibrillation. They noted that the absolute QT interval was not necessarily proportional to mortality risk and indeed, that the QT interval was actually normal (<440ms) in several patients with documented syncope, Torsade de pointes and family history. This was an important observation, as we now know that there is considerable overlap in the QTc intervals of controls versus LQTS mutation carriers.

The early to mid nineties saw the most fundamental advances in the unravelling of the pathogenesis of LQTS. Genetic linkage studies performed by Mark Keating's group (Utah) in 1991 mapped a gene locus on Chromosome 11. In 1994, the first defects in KCNQ1, were isolated followed by studies in the genes KCNH2/HERG (encoding a voltage-gated potassium channel) and SCN5A (encoding a voltage-gated sodium channel) were identified as the cause of LQT2 subclass 2 and subclass 3 respectively. By 1994, with the discovery of potassium channel KCNQ1/4P1as the LQT 1 linked gene (KCNQ1) a molecular basis for the majority of congenital LQTS syndromes was established. With a growing awareness of the Long QT Syndrome amongst cardiologists, updated and more refined diagnostic criteria were published in 2014.

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Over the past fifty years, advances in the field of inherited cardiac arrhythmias have been rapid and substantial. However, as Ward demonstrated 1964, precise and accurate description of the phenotype remains key when dealing with novel diseases.

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References

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2005 marked the 25th anniversary of the International Long QT registry. The well-defined and phenotyped clinical pedigrees now contained in the registry (families from both North America and Europe) provided not just insights to the clinical natural history of the LQTS spectrum but also the biochemical material for genetic analyses. The ever-present transatlantic cooperation in the Long QT syndrome was further evident in 2013 with the publication of a joint Heart Rhythm Society / European Heart Rhythm Association statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. This most recent guidance endorsed the LQTS risk score model, the therapeutic use of beta-blockers with implantable cardiac defibrillators in selected cases and the use of specific genetic testing. Despite the extraordinary progress in the characterisation, pathophysiology and treatment of the Long QT syndrome over the short period of fifty years, questions still remain. Risk stratification remains imprecise. The advances in the molecular aspects of the disease have enabled mutation-specific risk assessment but it has also been demonstrated that the disease can be present or absent in the absence of QT-modifying single nucleotide polymorphisms act as a second hit to the mutation and either prolong or indeed shorten the QT interval. Of particular clinical importance, is the need to improve identification of the highest risk patients who would benefit from implantation of a cardiac defibrillator.

Over the past fifty years, advances in the field of inherited cardiac arrhythmias have been rapid and substantial. However, as Ward demonstrated 1964, precise and accurate description of the phenotype remains key when dealing with novel diseases.