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Title: Who should die of a broken heart? A genetic and electrocardiographic study in earthquake stress cardiomyopathy.

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Introduction

"Alas, my liege, my wife is dead to-night; Grief of my son's exile hath stopp'd her breath." - Lord Montague, Romeo and Juliet.

Astute observers of humanity have long known that you can die of a broken heart. Broken heart syndrome can be triggered by experiencing an acute physical or emotional stress. This makes it difficult to study the time course of the condition (as it is often hard to pinpoint the initial stress) and to investigate any genetic basis to the condition (as it is rare for a group of susceptible people to be exposed to the same stressor). Following the major Christchurch and Kaikoura earthquakes, Christchurch Hospital has seen three unprecedented case clusters of broken heart syndrome, providing a unique opportunity to investigate both the time course of the condition and genetic susceptibility.

Aim

To extend previous work in Christchurch investigating the relationship between rare DNA copy number variants (CNVs) and broken heart syndrome in the earthquake-associated case clusters.

To undertake the definitive time-course study in broken heart syndrome based on having to-the-minute timing available for each of the earthquakes.

Impact

An understanding of the genetic basis of the condition would aid in identifying the underlying pathophysiology, which would be beneficial for treatment and research.

Knowing how relevant clinical signs change over the course of the condition may provide useful information about when mortality risk is the greatest and may guide new recommendations on clinical management. QTc prolongation is often observed in this condition. As QTc prolongation is the substrate for torsades de pointes (an often-fatal ventricular tachycardia), establishing the time after stress when peak QTc is reached will be an important finding.

Method

The Cardiology Department at Christchurch Hospital prospectively maintains a log of broken heart syndrome cases extending back to 2006.

Five cases associated with the Kaikoura earthquake of November 2016 were identified from this case log. These patients were contacted, and all agreed to travel to Christchurch where they were consented, before completing psychological questionnaires and providing a blood sample for genetic analysis. The DNA was extracted from the blood and array CGH analysis was carried out using Aligent 180k oligo arrays to detect the presence of CNVs. The data was analysed using PerkinElmer's Genoglyphix software, which allowed comparison of the patient's CNVs with

various disease and control databases to provide an indication of prevalence and potential clinical significance. This study was an extension of an earlier Christchurch study of 28 patients who presented with broken heart syndrome after the September 2010 and February 2011 Canterbury earthquakes. The CNVs identified in the Kaikoura earthquake cohort were compared with the CNVs identified in the 2010 and 2011 earthquake cohorts.

A total of 33 cases presented in three clusters after the September 2010, February 2011, and November 2016 earthquakes. ECGs and troponin results were reviewed from the duration of their hospital admissions, using both the hospital electronic record system and paper notes. The heart rate, PR interval, QRS width, and QTc interval were electronically and manually measured. Where the measurements were reasonably concordant the electronic measurement was used. Disagreement was resolved by a third-party measurement. T wave axis was electronically measured. All echocardiograms were over-read by a specialist Echocardiologist blinded to the clinical report. Where more than one echocardiogram for the admission was available, the one with the lowest LVEF was selected for inclusion.

Results

Two of the 5 patients had rare CNVs of uncertain clinical significance. One patient had a 50kb duplication at Xp22.2, a region containing the gene CA5B, which encodes mitochondrial carbonic anhydrase. The other patient had a 348kb duplication at 7p21.1, a region containing the genes AHR and KCCAT333. AHR codes for the aryl hydrocarbon receptor, which is involved in the regulation of xenobiotic-metabolising enzymes like cytochrome P450, neuronal development, and the toxic response. It is highly expressed in the heart and brain. KCCAT333 is a transcription factor and, though its effects on relevant genes is unknown, it may be of some significance.

Patients with a classic takotsubo pattern were found to have lower ejection fractions than those with a variant pattern, 36% vs. 44%, $p<0.0001$. The degree of myocardial damage as assessed by troponin was not correlated with the development of electrical abnormality, for correlation coefficient with peak QTc was -0.0971. The time courses for the changes in troponin and QTc were significantly different. Troponin level fell exponentially from a peak that occurred within 12 hours, whereas QTc was still increasing out to 48 hours.

Conclusion

Our finding of only two CNVs of uncertain significance suggests that previous work has overestimated the relevance of copy number variation in the genetics of the syndrome. This is consistent with previous research supporting a polygenic aetiology.

Often patients with an acute cardiomyopathy are discharged from hospital when their troponin has peaked. Our time course data shows that in broken heart syndrome electrical changes are discordant from the myocardial damage and will highlight for clinicians the importance of considering longer periods of ECG monitoring.