Brugada Syndrome

Genetics – 10 years later

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Running title: Genetics and Brugada syndrome

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Since its initial description in the early nineties, Brugada syndrome has attracted progressively more attention in the cardiology community. There are many reasons for it becoming such a focal point. First, the disease takes the life of individuals in their forties, during the most productive years. Second, the delineation of the disease coincided with a burst of activity in the molecular biology in the field of cardiology. We are at the beginning of a golden age in research of molecular cardiology with the Human Genome Project. Familial diseases will benefit greatly from advances in the field. Third, once thought to be rare, the Brugada syndrome is now recognized to have a relatively high incidence in parts of the world, particularly the Southeast Asia. Thus, the past decade has witnessed a rapid growth in our understanding of the cellular and genetic basis of Brugada syndrome. Research involving the characteristics of the action potential in ventricular myocardium using arterially-perfused wedge preparations and the identification of the first gene responsible for the disease; have contributed to many of these advances.

Basic research into the mechanisms underlying the Brugada syndrome is in its infancy and the next ten years will probably provide still better understanding of this lethal disease. What started as an electrocardiographic curiosity has become a great challenge for electrophysiologists, cardiologists, biophysicists and molecular biologists.

GENETICS

A definitive link between the sodium currents and Brugada syndrome has been provided by research in genetics. The first gene responsible for the disease was identified in 1998 by Chen and coworkers[1]. This gene, the a-subunit of the cardiac sodium channel gene, SCN5A, is responsible for the phase 0 of the cardiac action potential. The identification of mutations in SCN5A causing the disease and the decrease in availability of

sodium ions, suggest that a shift in the ionic balance in favor of I_{to} during phase 1 of the action potential is the determinant of the disease[2].. To date, this is the only gene linked to Brugada syndrome. SCN5A has been identified in approximately 25 % of the patients with Brugada syndrome, indicating that there is at least another gene responsible for the disease. In 2002, a second locus, on chromosome 3 was identified, although the gene responsible has not been identified as yet [3]. Close to 60 different mutations in SCN5A have been reported to date and approximately half of them have been biophysically characterized. The common denominator in the analysis of the mutations is the decrease in Na current availability by two main mechanisms: lack of expression of the mutant channel, or acceleration of inactivation of the channel[4]. These are at this point considered the main pathophysiological mechanisms causing Brugada syndrome. In the case of T1620M mutation, the alteration in the ionic currents worsened at higher temperatures[5]This too may have some clinical correlation as there have been several cases of ventricular fibrillation in patients with Brugada syndrome that develop during febrile states[6-8]..

Brugada syndrome is usually a disease which affects individuals in their forties. However, it has also been described as causing sudden infant death syndrome (SIDS)[9]. In addition to Brugada syndrome, mutations of SCN5A can lead to a large spectrum of phenotypes, including long-QT syndrome (LQT3)[10], isolated progressive cardiac conduction defect[11], idiopathic ventricular fibrillation[1], and sudden unexplained nocturnal death syndrome (SUDS or SUNDS)[12]. These are all considered allelic diseases, caused by mutations in a same gene. Electrocardiographic, clinical and biophysical data have clarified the relationship between these diseases in part.

When comparing to LQT3, Brugada syndrome could be considered a mirror image. Biophysical data indicates that LQT3 mutations cause a delayed inactivation of the channel[10], which is exactly the opposite as

in Brugada syndrome, where there is an accelerated inactivation[5]. The difference between the two diseases is however difficult to identify in some cases, and one family has been described manifesting the phenotype of both Brugada and long QT syndromes[13]. Likewise, the line between progressive conduction disease and Brugada syndrome is closer than ever after the publication of a paper with a family displaying both diseases[14]. Whether they represent variable phenotypic expression of the same disease is difficult to ascertain. One thing appears to be true, all the affected family members in this family, with Brugada syndrome or conduction disease, have a mutation that has proven lethal to some of its members. This certainly raises important issues regarding therapy, prevention and risk stratification.

Recent studies have shed some light on the distinctions or lack thereof between Brugada syndrome and Sudden Unexpected Death Syndrome (SUDS) in Southeast Asia. SUDS is very prevalent in Southeast Asia. In countries like Thailand, it is believed to affect up to 1% of the population, and it is the most common cause of death in young males, second only to car accidents[15]. The patients commonly die at night and the male to female ratio is on the order of 10:1. Electrocardiographically, the disease is identical to Brugada syndrome. It is also caused by mutations in SCN5A and biophysical data indicates a non-working SCN5A or accelerated inactivation[12]. These characteristics are similar to those of the Brugada syndrome, suggesting that they are the same disease.

CONCLUSIONS

The past decade has witnessed the identification of a new clinical entity responsible for sudden death in the young and the evolution of a strategy to diagnose, risk stratify and treat patients with this syndrome. This has been possible thanks to the efforts of many centers around the world and to the collaboration of hundreds of physicians. This is still a very new disease, with a high social impact due to the fact that it involves death of relatively young individuals. Through research and continued collaboration among the basic and clinical groups involved, we look forward to advances that will enable us to better identify those at risk and provide the means to treat them more effectively, so as to reduce the burden of this disease on the affected families.

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