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Updated in Genetics of Drug-Related Arrhythmias

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Abstract

In modern medicine, Adverse Drug Reactions (ADRs) are an emerging field and some genetic mutations can cause ADRs. Among those, an arrhythmic clinical picture might be due to mutations in genes encoding either sodium, calcium or potassium channels. In such cases, the adverse drug reaction can be either dose dependent or independent with a variable risk of sudden cardiac death generally higher than in general population. In such cases there is an increasing evidence about the pivotal role of genetic testing for prevention and therapeutic optimization. Today, even a pre-symptomatic genetic testing for drug-induced arrhythmias is a useful tool for clinicians with a very good cost-benefits ratio. This chapter is focused on the most common drug-related arrhythmias, on their genetic causes to the best of current knowledge (updated on January 24th 2021) and on possible future directions in this field.

Keywords: Drug-Related; Precision Medicine; Arrhythmia; Long QT syndrome; Brugada Syndrome.

Abbreviations: ADR: Adverse drug reactions; NSAIDs: Non-Steroidal Anti Inflammatory Drugs; BrS: Brugada Syndrome; LQTS: Long QT Syndrome; NGS: Next generation sequencing.

Introduction

In spite of great technical improvements, the genetic causes of ADRs are still not completely elucidated. In fact, the complexity of this topic and the cost of suitable analysis, prevent a large employment of genetic testing before the administration of a potentially harmful drug. This is relevant because the clinical picture associated with adverse drug reaction might virtually involve every organ. This is translated clinically in a consistent length of hospital stays, with a very high costs for the healthcare service [1]. Many statistical analyses reported that more than one hundred thousand people yearly die for because of ADRs especially in US. Many of those people die suddenly for cardiac arrhythmias where ventricular involvement is the most common clinical presentation, but thrombotic events and anestesiologic issues are not rare. The sensitivity of the heart to drugs can be explained by many peculiar factors like coronary circulation, presence of specialized tissues with many diverse metabolic features and modulation of gene expression during patient's life. Is beyond the aim of this chapter to talk about the metabolic differences between myocardium and heart conduction system but it has to be mentioned that in clinical settings these considerations can influence therapeutic management and prognosis. An adverse drug reaction is a harmful and unintended response to the administration of a certain drug at therapeutic dosage. In particular, to the best of current knowledge, the mechanism of ADRs can be either dose dependent or dose independent. In the first case, there is a linear correlation between drug's concentration and clinical picture. This means that the clinical picture tends to worsen when the drugs' dosage increases. An example of this can be the Q-T trait prolongation after antibiotics, antipsychotic or other commonly used

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drugs. On the other side, when there is a dosage independent ADR, the clinical picture tends to persist regardless of drug's dosage. This kind of ADR can be observed, for example, in the J point elevations after the administration of general anesthetics. Both of Q-T prolongation and J point can have a genetic background: Single - copy mutations in *SCN5A, KCNQ1, CACNA1C* or *KCNH2* are commonly found in such cases.

General key points

About 5% of patients affected by arrhythmias and treated with drugs can be affected by adverse drug reactions involving the heart[2]. The most common anti-arrhythmic drugs are flecainide, Sotalol and Propafenone: Each one can be associated with either J point elevation, Q-T trait prolongation or other kinds of arrhythmias. In those cases, it might be not easy to distinguish between pre-existent arrhythmias and drugs' effects. Genetic testing can be helpful for this purpose because a few mutations in sodium, calcium or potassium genes can explain a relevant part of these cases. Moreover, a feasible identification of patients potentially at risk to experience drug - related heart problems is mandatory to improve therapies and prognosis, especially during the SARS-CoV-2 pandemic. Another group of patients is treated with non-cardiovascular drugs like antibiotics, painkillers, NSAIDs, mood modulators and others. Of note, in such cases, the main effect of the administered drug does not involve the heart itself. In spite of this, a variable percentage of such patients can experience drug-related arrhythmias due to the same aforementioned genetic mutations [2]. In summary, an arrhythmic ADR might happen in two different kind of patient sharing the same genetic background. This is the main reason to spend both money and time studying these mutations, as, even though we have already discovered multiple genomic variants which can be responsible of these arrhythmogenic drug reactions, many variants still go undetected and tests are at the moment too expensive to be performed on all patients who are administered with these drugs. Another point that has to be brought up is that, with the currently available means, clinical diagnostic tools such as the electrocardiograph and the pharmacological tests are still more sensitive and more specific than genetic testing. In fact, long QT syndrome is confirmed in only 75% of cases with genetic testing and Brugada syndrome is confirmed in only around 30% of cases with a molecular test, for rarer arrhythmogenic conditions such as short QT syndrome it is even less [3]. These test however have a strong role in assessing the familiarity and thus the recurrence rate of these syndromes, as well as aiding in treatment in the case of LQTS [4-6]. On top of this, a recent publication has shown the potential benefits of genetic classification for prognostic and thus therapeutic purposes also in Brugada syndrome [7].

Drug-induced QT prolongation and long QT syndrome

Many different drugs can interact with heart conduction system resulting in a prolonged QT trait in basal twelve derivation ECG. It is proven that congenital long QT syndrome and drug related Q-T trait prolongation often share the same genetic background. That said variants characteristic of LQTS are sometimes seen in the general population with still effect that haven't yet been investigated [8], moreover, mutations in the NOS1AP gene have been found to be related to drug induced QT prolongation but not to classic forms of LQTS [9]. Drugs widely used for infections, epilepsy, mood disorder, metabolic diseases and arrhythmias can prolong the Q-T trait in standard ECG as a harmful and unintended response to their administration [10-13]. The recognized mechanism of such ADR is the block of potassium channels, which is strictly dose - dependent and can result in the sudden onset of major ventricular arrhythmias, like Torsade de Points (TdP). The website www.qtdrugs.org contains a daily updated list of drugs associated with this kind of QT prolongation. About 75% of patients affected by drug induced QT prolongation harbour mutations, of all genetic confirmations, 90% are found in one of three major genes, all identifiable today with specific laboratory techniques like Next Generation Sequencing approach (NGS). Differently from Sanger sequencing, NGS allows to analyze many genes at the same time. Those genes encode for either potassium (*KCNQ1, KCNH2*) or sodium (*SCN5A*) channels [14]. In such individuals, the basal QT trait might be normal but tends to prolong after the administration of specific drugs. This kind of adverse drug reaction is more common in females, after sport, after sleep and in particularly stressful situations; these triggers all share a change in the autonomic state, leading to think that the sympathetic tone could play a role in these factors [15]. A continuously updated list of QT prolonging drugs can be found at the website https://crediblemeds.org/. It is possible to describe some useful genotype-phenotype correlations as follows. First of all, patients with one mutation in *KCNQ1* usually have T wave abnormalities at basal ECG while patients with two mutations in this gene can also be affected by deafness although in these cases we are talking about Jervell and Lange-Nielsen syndrome, which is a genetic syndrome which occurs when with a mutation in both alleles of *KCNQ1* [16]. *KCNH2* gene is instead less common: Patients with one mutated copy of this gene can display a huge variety of ADRs, often with either syncopal or lipothimic episodes [17]. In patients with single copy mutations in *SCN5A* the adverse event happens during the rest or even while sleeping. The carriers are at risk also for other kind of heart problems like Brugada syndrome, early repolarization or ventricular dysplasia [18]. Four other genes (*CALM1, CALM2, CALM3, TRDN*) can cause drug related QT trait prolongation but less commonly than the other three.

Drug-induced brugada pattern and brugada syndrome

A drug induced arrhythmia can be part of the phenotype of Brugada Syndrome (BrS). This condition is diagnosed by a typical association of ECG signs when the coved-type ST-segment elevation in the right precordial leads is very important. BrS is associated with an increased risk of Sudden Cardiac Death (SCD) compared to general population. BrS is still considered a genetic disease but genetic testing fails to confirm the clinical diagnosis in about 70% of patients [19]. The ECG signs of BrS can be either spontaneous or induced by various drugs. In such cases the mechanism of the adverse drug reaction is the sodium channel's blocking, this reaction can be either strictly dose - dependent or completely dose- independent [20-22]. This is why all patients affected by BrS should avoid a list of drugs, downloadable at http://www.brugadadrugs.org/. The major Brugada gene is *SCN5A* but at least other 24 genes are disputed as a possible alternative molecular causes of this phenotype. Of note, Brugada syndrome is frequently associated with atrial fibrillation, whose therapeutic agents such class IC drugs (Flecainide and Propafenone) can unmask cases of latent or undiagnosed Brugada syndrome.

Summary and conclusions

Adverse Drug Reactions (ADRs) remain even today an important cause of both morbidity and mortality all over the world. The technical improvement of genetic testing in the last ten years allowed the identification of multiple genes involved in ADRs.

This new knowledge led to the definition of clinically useful pharmacogenetics: The safe therapeutic use of many common drugs can be optimized using NGS approach for genetic testing. The main genes to be studied are *SCN5A (*associated with either LQTS or Brugada syndrome), *CACNA1C*, *KCNQ1* and *KCNH2.* The interplay between clinicians and researchers will improve further this kind of genetic testing, giving a future possibility to avoid or even to prevent many harmful drug-related arrhythmias.

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