Point of view

Schizophrenia: if death occurs without warning, what we should propose for the near future?

Esquizofrenia: se a morte acontece sem aviso prévio, o que devemos propor para o futuro próximo?

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Thomas Alva Edison, an American inventor, scientist and businessman: *If we all did the things we are capable of, we would astound ourselves.*

Sudden cardiac death (SCD) is the most common lethal manifestation of heart disease, and in many cases it is the descent's first and only symptom[1-3]. SCD is defined as "unexpected natural death from a cardiac cause within a short time period, generally ≤ 1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal"[3]. Actually, clinical and pathologic findings suggest that patients with conditions such as coronary artery disease, cardiomyopathy, cardiac rhythm disturbances, or hypertensive heart disease are at high risk of SCD[4,3]. From epidemiological point of view, the current annual incidence of SCD in the United States (total population approximately 300 000 000) would range between 180 000 and 250 000 cases per year. For the world (total population approximately 6 540 000 000), the estimated annual burden of SCD would be in the range of 4 to 5 million cases per year[5]. Due to this scenario, SCD is considered a major unsolved problem in clinical cardiology, emergency medicine, and public health system[3].

Transiting the field of schizophrenia, the topic of SCD should not be overlooked. With this in mind, a series of data could be put forward to explain it.

Although schizophrenia has been considered a distinct disease entity for many decades, its precise definition and etio-pathophysiology remain obscure and its treatment remains unsatisfactory. Schizophrenia is increasingly being viewed as a neurodevelopment disorder likely multi-factorial in origin[6]. In these aspects, schizophrenia is a chronic and devastating brain disease characterized by a collection of signs and symptoms such as psychosis, severe impairments in cognition, behavior and affect, as well as impairments in the ability to work, have a family and socialize[7,8].

Whereas pharmacotherapy is still considered an important approach to treating schizophrenia, many patients continue quite symptomatic and remain cognitively and functionally impaired despite optimal treatment. Indeed, approximately 30% of individuals with schizophrenia exhibit little or no improvements with antipsychotics[9]. This problem of minimal improvement in multiple symptom and functional domains despite contemporary treatments is further compounded by the fact that patients with schizophrenia have a high rate of premature death compared with the general population. Studies have found that individuals with schizophrenia have a two to three-fold greater risk of premature death than individuals without schizophrenia. It has been hypothesized that this increased risk of early death may be due to many factors including life style, suicide (in particular in young male patients within the first decade after diagnosis), early development of cardiovascular disease, and high prevalence of metabolic syndrome and carbohydrate and lipid metabolic disorders. An equally and unfortunately deemphasized cause of premature death in patients with schizophrenia is sudden cardiac death[7,10-15]. In these lines, understanding the mechanisms and possible causal factors behind sudden cardiac death in individuals with schizophrenia is crucial for establishing preventive measures.

There is evidence that cardiovascular dysfunction is directly associated with the occurrence of abrupt fatal events in these individuals[13,14,16]. First, some antipsychotics have been associated with cardiovascular adverse events (*e.g.*, QT interval prolongation), suggesting that this could lead to torsade the points or sudden death in schizophrenia patients[13-17]. Second, several antipsychotic agents are associated with metabolic dysfunction, including diabetes mellitus, increased triglyceride levels and weight gain, all of these factors have been associated with increased cardiovascular risk[16,18,19]. Third, antipsychotic treatment has been linked with alterations in blood pressure and heart rate, among which orthostatic hypotension, with or without syncope, is relatively common[16,20,21]. Fourth, smoking is also considered an important risk factor for sudden cardiac death in people with schizophrenia and the effects of smoking on cardiac system may be due to an increase in platelet adhesiveness and release of cathecholamines[7,22].

Despite scientific advances in recent decades, it has been extremely difficult to prevent the occurrence of sudden cardiac death in individuals with schizophrenia, largely because there have been no concerted or coordinated efforts to address this major public health problem. One possibility would be to emulate successful programs in other areas of medicine towards the area of sudden cardiac death. For example, the sudden unexpected death in epilepsy (SUDEP) research program developed by Devinsky and Friedman in 2011 has been successful program in reducing premature death from epilepsy[23,24]. Implementing a similar program in patients with schizophrenia would be with the goal of reducing or even preventing sudden cardiac death in schizophrenia. Such efforts would include: (1) Clinical and research collaborations to incorporate the expertise and knowledge of various medical and research specialties and other health related areas. These collaborations would hopefully culminate into multidisciplinary research which is essential for developing novel therapeutics, unraveling the mechanisms of premature cardiac death, and identifying specific causal factors and preventive measures to minimize the occurrence of sudden cardiac death in schizophrenia. (2) Create data collection systems to obtain prospective data from treatment centers, clinicians, patients and their families. These data can then be further analyzed to identify risk factors for the occurrence of sudden cardiac death in schizophrenia thus producing a direct measure of risk. Furthermore, it would be appropriate to develop additional prospective studies in reference centers in psychiatry using cardiac physiological parameters to try to assess more precisely our understanding of the cardiovascular alterations that affect individuals with schizophrenia in order to reverse or avoid a fatal cardiac event. (3) Preclinical studies could be conducted to better understand risk factors, mechanisms, causes and preventive measures. Due to the

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difficulty in establishing the precise cause or causes of sudden cardiac death in schizophrenia, animal models may be a suitable model for investigating possible underlying pathophysiological mechanisms[25]. It would be then important to integrate these findings from basic science with clinical studies also known as "bench-to-bedside" research[26]. (4) Implement interventions prospectively which resulted from the above efforts to determine their utility in preventing the occurrence of cardiovascular changes that may culminate in sudden death in individuals with schizophrenia. Clearly, it would be paramount that these procedures be instituted when the initial diagnosis of schizophrenia is made.

Currently, our understanding of the best strategies in preventing sudden cardiac death in schizophrenia is still in its infancy. Initial data suggests that preventative measures other than medical therapies could be useful in reducing the risk of sudden cardiac death in schizophrenia[9], although strict evidence for their effectiveness is still lacking.

Although we have not tabulated epidemiological data on cases of SCD in individuals with schizophrenia in our facility, many of our psychiatrists have reported the occurrence of fatal events among our patients, reinforcing that schizophrenia-related mortality, particularly sudden cardiac death, is a significant public health concern at a global level. It is crucial that a concerted and collaborative approach be implemented to tackle this worrisome problem. Based on the success of the SUDEP[23,24] program, we believe that a similar program could be instituted for reducing the risk of or preventing sudden cardiac death in patients with schizophrenia. Resulting data from this program could then be prospectively tested in patients with schizophrenia to determine their effectiveness in preventing or minimizing the occurrence of sudden cardiac death.

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