SUDEP research without walls

The creation of a virtual Center Without Walls to study sudden unexpected death in epilepsy (SUDEP) was announced by the US National Institute of Neurological Disorders and Stroke (NINDS) on Dec 8, 2014. For the epilepsy community—at that time gathered in Seattle, WA, USA, for the Annual Meeting of the American Epilepsy Society—the announcement of this new initiative signals the onset of an exciting period in epilepsy research. Large collaborative research initiatives are needed to shed light on the risk factors and mechanisms that can lead from epilepsy to premature death, and the creation of this new Center Without Walls will accelerate progress over the coming year.

Nine research teams form the new Center Without Walls, with a budget of less than US$6 million at present. Investigators will share data and resources to address SUDEP from several angles: from the study of underlying brainstem pathways to the associated respiratory and cardiac dysfunction, and from neuropathological analyses to the assessment of genetic susceptibility. NINDS should be commended for prioritising this area of epilepsy research. The risk of sudden death is about 20-times higher in people with epilepsy than in the general population. Incidence ranges from 0·09 per 1000 person-years in newly diagnosed patients to 9·3 per 1000 person-years in candidates for epilepsy surgery. However, sudden death is a major concern not only in people with pharmacologically intractable epilepsy (who have an estimated 35% lifetime risk), but also in adult patients in whom epilepsy is not fully controlled, in patients with predisposing mutations, and in children with Dravet syndrome. In the USA alone, there are about 3000 cases of SUDEP each year. Understanding the genetic, physiological, and environmental risk factors behind such increased mortality will lead to preventive strategies that can help to tackle these dismal figures.

A few years ago researchers proposed a unified definition of SUDEP that integrates the several variations used in studies over the past two decades. This definition classifies SUDEP as a “sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death, occurring in benign circumstances” in a patient with or without seizures, and without status epilepticus. Early onset of epilepsy and young adult age are well established risk factors for SUDEP; poor seizure control, particularly generalised tonic-clonic seizures, is a modifiable risk factor. But because of the diverse definitions of SUDEP used in previous studies, and because most of these studies had fairly small sample sizes and methodological limitations, the importance of other proposed risk factors is still debated. In view of the absence of robust evidence and the uncertainties about potential risk factors, many clinicians avoid discussion of SUDEP with their patients, even though most epilepsy specialists would agree that people at high risk (such as those with refractory epilepsy) should be informed.

The striking findings from the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) exposed the need for changes in clinical practice even in tertiary centres. This large, multicentre, retrospective study investigated mechanisms of SUDEP in thousands of patients who underwent video EEG in 147 epilepsy monitoring units. This pioneering approach established a common pattern of SUDEP, which is referred to as an “early postictal neurovegetative breakdown”. SUDEP was triggered by a generalised tonic-clonic seizure, usually followed by rapid breathing, and eventually ending in cardiorespiratory collapse; in those cases in whom postictal cardiorespiratory function was partly restored, terminal apnoea always preceded cardiac dysfunction. Notably, all patients in whom cardiorespiratory resuscitation was done within 3 min of the cardiac arrest survived, and 14 out of 16 cases of SUDEP recorded in this study occurred during night shifts, when clinical supervision might have been suboptimum. Also of concern, the incidence of SUDEP in these monitoring units (about 5·1 cases per 1000 patient-years) pointed to antiepileptic drug withdrawal as a cause of SUDEP, and was similar to the incidence in patients with refractory epilepsy out of hospital, emphasising the urgent need for methods to predict sudden death.

The new Center Without Walls to study SUDEP could greatly advance the understanding of mechanisms and risk factors gained from MORTEMUS and other studies, and should pave the way for the necessary prevention strategies in the clinic and in the population. The epilepsy community will have the opportunity to discuss their progress in December, 2015, in Philadelphia, PA, USA, at the next Annual Meeting of the American Epilepsy Society. Hopefully, the progress will be such that NINDS and other funders will be compelled to increase support for SUDEP research.