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The brain-heart connection: Implications for understanding sudden unexpected death in epilepsy

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Abstract

Epilepsy is one of the commonest neurological problems worldwide. Approximately 3% of the general population will suffer from epilepsy at some point in their lives. Unfortunately, individuals with epilepsy are at a higher risk of death than the general population, and sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. Information concerning risk factors for SUDEP is conflicting, but potential risk factors include young age, early onset of epilepsy, duration of epilepsy, uncontrolled seizures, seizure frequency, antiepileptic drug number and winter temperatures. Although the cause of SUDEP is still unknown, its most commonly suggested mechanisms are cardiac abnormalities during and between seizures. As the anatomical substrate of epileptic activity in the central nervous system shows a direct relation to cardiovascular alterations, this may suggest that patients with epilepsy associated with focal central nervous system lesions may face a particular risk of SUDEP. Currently, experimental and clinical data supports the importance of specific brain structures in the behavioural manifestation, the initiation and the propagation of seizures. Regarding the above findings, our research group focused on this review article that SUDEP could be related to the occurrence of specific brain structure dysfunction or anatomical change, at least in some cases. (Cardiol J 2009; 16, 5: 394–399)

Key words: epilepsy, sudden cardiac death, heart, central nervous system

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Epilepsy: General view

The epilepsies are one of the most common serious brain disorders, present in approximately 50 million people worldwide [1]. In the US, about 100,000 new cases per year of epilepsy are diagnosed [2, 3]. In the UK, between 1 in 140 and 1 in 200 people (at least 300,000 people) are currently being treated for epilepsy [4]. Epidemiological studies suggest that 70% to 80% of the people developing epilepsy will face remission, while the remaining patients will continue to have seizures and are refractory to treatment with the currently available therapies [5–7]. The commonest risk factors for epilepsy are cerebrovascular disease, brain tumours, alcohol, traumatic head injuries, cortical development malformations, genetic inheritance, and central nervous system infections. In resource-poor countries, endemic infections such as malaria and neurocysticercosis seem to be major risk factors [8]. Epilepsies are characterized by spontaneous recurrent seizures, caused by focal or generalized paroxysmal changes in neurological functions, triggered by abnormal electrical activity in the cortex [9]. Because it involves hyper-excitable neurons, a basic assumption links the pathogenesis of epilepsy and the generation of synchronized neuronal activity to an imbalance between inhibitory (γ-aminobutyric acid [GABA]-mediated) and excitatory (glutamate-mediated) neurotransmission, in favour of the latter [10]. Seizures and epilepsy are usually subdivided into two groups: the partial and the generalized. The partial or focal seizures show clinical or electroencephalogram (EEG) evidence of a local onset and may spread to other parts of the brain, while the generalized seizures begin simultaneously in both cerebral hemispheres [8].

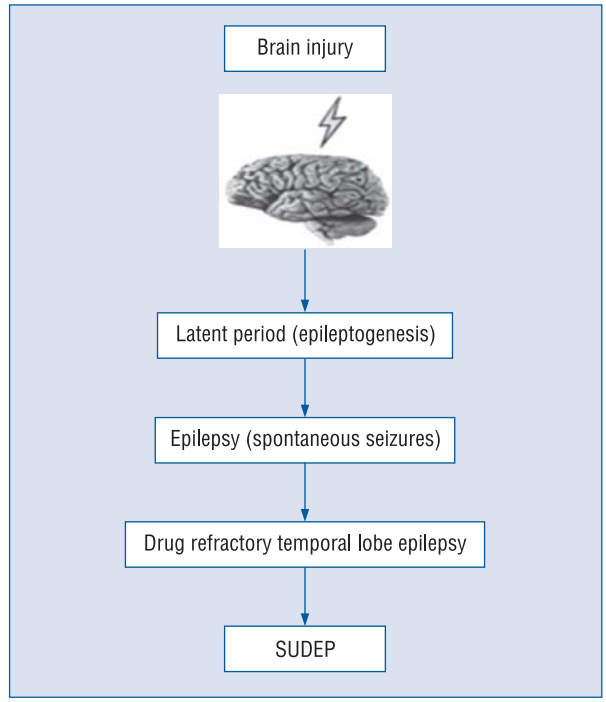

Figure 1. Brain injury leads to abnormal structural and functional reorganization of the brain circuitry. During this time (latent period), circuitry reorganization leads to permanent hyperexcitability and the occurrence of recurrent spontaneous seizures. Temporal lobe epilepsy is the most common form of drug-refractory epilepsy and sudden unexpected death in epilepsy (SUDEP) represents the leading cause of mortality in adults with refractory epilepsy.

Sudden unexpected death in epilepsy

Introduction

Each year, around one in 1,000 patients with chronic epilepsy die suddenly, unexpectedly, and without explanation, even after post-mortem examination [11]. This phenomenon is called sudden unexpected death in epilepsy (SUDEP) (Fig. 1) [11]. Thus, we have considered that epilepsy is associated with a two- to three-fold increase in mortality when compared to the general population, and SUDEP is the most important direct epilepsy-related cause of death [8]. Although early mortality series reported deaths from status epilepticus were more common at the beginning of the 20th century, those associated with SUDEP were also recognized [12]. Accordingly, Spratling [13] described in 1904 how epilepsy "destroys life suddenly and without warning through a single, brief attack... and does so in 3% to 4% of all who suffer from it".

Definitions

The lack of autopsy findings and the rarely witnessed cases of SUDEP pose difficulties in defining SUDEP. In general terms, SUDEP is defined by the precise criteria that were approved in 1997 by an expert panel: as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which *post mortem* examination does not reveal a toxicological or anatomical cause of death [14].

Incidence

The incidence of SUDEP varies due to differences in the population study, the documentation

level and the SUDEP definitions [15]. Today, SUDEP is responsible for 7.5% to 17% of all deaths in epilepsy and has an incidence of 1:500 to 1:1,000 patient-years among adults [16].

Risk factors

The knowledge of the risk factors that underlie SUDEP could guide the investigations of its pathophysiological mechanisms [17]. Likewise, understanding those mechanisms may lead to the identification of previously unrecognized risk factors that are more amenable to correction [17]. Currently, a number of factors associated with SUDEP have been reported, but the results are not entirely consistent among the studies. Those include refractoriness of the epilepsy, presence of generalized tonic-clonic seizures, polytherapy with antiepileptic drugs, young age, duration of the seizure disorder (ranging from 15 to 20 years), early onset of epilepsy and winter temperatures [15, 18].

Mechanisms

Understanding the mechanisms behind SUDEP is key to its prevention [12]. Different mechanisms are probably involved in SUDEP when individual cases are considered [15]. Cardiac mechanisms, such as repetitive cardiac damage and arrhythmia during seizures are possibly triggered by apnea and/or cerebral autonomic imbalance, with sympathetic overstimulation [15, 19]. Many authors have suggested that the autonomic nervous system (especially the sympathetic system) may have been involved in the development of fatal arrhythmias [19, 20]. Furthermore, undetected cardiac or respiratory diseases predisposing for arrhythmias or apnea may have played a role in SUDEP [15]. Although potential pathomechanisms for SUDEP are unknown, it is very likely that cardiac arrhythmia during and between seizures play a role in this matter [15, 21]. A number of post-mortem, ictal and interictal cardiac abnormalities account for the possibility of seizure-induced cardiogenic SUDEP [15, 22].

Post-mortem examinations in people killed by SUDEP have shown a more dilated and a heavier heart than expected [15, 23, 24]. Pulmonary edema was found in approximately 50–86% of SUDEP cases [15, 23, 24]. Furthermore, some pathological alterations in the heart in SUDEP cases have also been described, such as: small coronary artery wall fibrosis, atrophy of cardiomyocytes, myofibrillar degeneration, edema of the conductive tissue and morphological abnormalities of the cardiac conduction system [15, 23, 24]. These abnormalities may have been the consequence of repeated hypoxemia and/or have been associated with the increase of catecholamines during ictal sympathetic system storm [15, 23, 25].

Several studies assessed the frequency and character of ictal cardiac rhythm during seizures [15, 22, 23, 25] and the most compelling evidence derived from the presence of ictal arrhythmias [22]. For instance, Nashef et al. [26] recorded non-invasively ictal cardiorespiratory variables in patients with epilepsy. They found a 91% increase in the heart rate from 41 monitored seizures, and a transient bradycardia in five seizures (four patients) [26]. Moreover, Nei et al. [27] evaluated the electrocardiographic (ECG) changes in 51 seizures from 43 patients with refractory epilepsy. They showed that 70% of patients had either had ECG abnormalities (16%) or tachycardia (30%) or both (23%) during ictal and/or post-ictal period. The authors suggested that those changes may have been relevant to SUDEP pathophysiology [27].

Some research groups have described cardiac investigations between seizures. Drake et al. [28] reviewed resting ECGs from 75 patients with epilepsy and compared the ventricular rate, the PR interval, the QRS duration and the QT interval corrected for heart rate (QTc) with the normal ECGs recorded from age-matched patients without cardiac or neurological disorders. Epilepsy patients showed a higher heart rate and a longer QT duration than those from ECG recorded age-matched patients without a cardiac or neurological disorder. However, heart rate and QT duration were not outside the normal range [28]. In 2003, Tigaran et al. [29] investigated whether patients with drug refractory epilepsy had cardiovascular abnormalities that might have been related to a high frequency of sudden death. In their study, 23 subjects underwent comprehensive cardiovascular evaluations (ECG, Holter-monitoring, echocardiography, ergometric exercise test, myocardial scintigraphy and coronary angiography, whenever abnormalities were found) before and during video--EEG monitoring. They found a ST-segment depression in 40% of the cases associated with a higher maximum heart rate during seizures, suggesting that a cardiac ischemia may have occurred in those patients [29]. Although interictal changes in heart rate variability have been described in patients with epilepsy, their contribution to SUDEP remains to be determined.

The role of brain-heart connection

Elucidating risk factors and establishing SUDEP mechanisms are very important in deve-

loping prevention methods. Of the many risk factors suggested for SUDEP, cerebral mechanisms or transmission of epileptic activity via the autonomic nervous system to the heart, play an interesting role in this scenario. An increase in the sympathetic nervous discharge leads to increased secretion of adreno-medullary catecholamines and to reduced parasympathetic activity, facilitating the occurrence of supraventricular and ventricular arrhythmias that are observed in cerebrogenic diseases [19].

It has long been believed that in the healthy brain the stimulation or the lesion of some central nervous system structures is able to promote morphological and functional cardiovascular alterations [30]. As the anatomical substrate of epileptic activity in the central nervous system shows a direct relation to cardiovascular alterations, this may suggest that patients with epilepsy associated with focal central nervous system lesions may be at particular risk of SUDEP [30, 31]. It has been shown that epileptic activity originating in some brain structures (amygdala, cingulated gyrus, insular cortex, frontopolar or frontoorbital regions) may have induced arrhythmias such as supraventricular tachycardia, sinus tachycardia, sinus bradycardia, sinus arrest, atrioventricular block and asystole [22, 32], which could have been implicated in SUDEP. In this respect, it was also shown that electrical stimulation of the pre-central operculum proved to elicit apnea in patients with epilepsy, whereas insults to the insular cortex appeared to promote cerebrogenic sudden death [22, 33, 34]. Furthermore, it is also interesting to note that despite the clear indications that the insular cortex regulates cardiovascular function in animals and humans, little data is available regarding its implication in severe ictal arrhythmias or SUDEP occurrence [22, 35, 36]. Willing to find the specific brain structures related to the cardiovascular abnormalities and hence SUDEP occurrence in patients with refractory epilepsy, our research group was the first to propose a possible role of the thalamus in some cases of SUDEP [37].

A possible role of thalamic nuclei in triggering and spreading epileptic discharges has been discussed over the last four decades [38], and current experimental and clinical data supports an important role for thalamic nuclei in the behavioural manifestations, the initiation and the propagation of epileptic seizures [39]. The importance of the thalamus in the genesis of epileptic seizures is related to its extensive projection to the cortex and to other areas, including the basal ganglia, cerebellum, and hippocampus [40, 41]. Though temporal lobe epilepsy (TLE) is the commonest form of partial epilepsy, and hippocampal atrophy and sclerosis are the most frequent abnormalities associated with TLE, brain structural changes in patients with TLE are not confined solely to the hippocampus. Indeed, they have been reported to occur in other brain regions, such as the parahippocampal region, entorhinal and perirhinal cortex [42–44]. Interestingly, a recent study has demonstrated thalamic atrophy in patients with TLE, which was more prominent in the thalamic nuclei that had strong connections with the limbic system [45]. Moreover, using the pilocarpine model of TLE, our research group also reported an important role of the posterior thalamus in the cerebral circuits of rats with epilepsy [46]. The first study investigated the interictal cerebral metabolic rate with ^{14}C-2DG autoradiography in chronic pilocarpine--induced rats and found an increase in the glucose utilization by several brain regions in epilepsy [47]. The most relevant finding was that of a consistent rise of cerebral metabolic rate in the lateral posterior (LP) thalamic nuclei, suggesting that the LP may have been involved in the cerebral circuitry controlling epileptic activity during interictal intervals. The second study evaluated the contribution of LP to spontaneous recurrent seizure activity induced by pilocarpine [46]. It was shown there that bilateral LP lesion by ibotenic acid in chronic epileptic rats resulted in an increase of seizure frequency, suggesting that LP was one of the most important thalamic nuclei involved in the inhibition of spreading mechanisms.

In accordance with the above-mentioned findings, is it plausible to propose that cardiovascular abnormalities, and hence SUDEP, could be related to the occurrence of lateral posterior thalamic morphological or functional changes, at least in some cases? As research in this field must be guided by the possible mechanism of SUDEP, a number of arguments might be put forward. From the morphological point of view, Boyko et al. [48] showed that bilateral injections of kainic acid into the thalamus, mainly in the lateral posterior thalamic nuclei, produced myocardial necrosis in adult rats, suggesting that this specific thalamic nucleus was directly related to the cardiovascular system. In the same way, it is very important to establish whether there is a relation between the lateral posterior thalamic nuclei dysfunction and the cardiac functioning. According to this, an experimental study developed by our group may have started to reinforce this idea. In 2005, we evaluated the *in vivo* heart rate (ECG) and isolated the *ex vivo* preparation (Langendorf preparation) of rats with epilepsy [49]. Our results showed significant differences in the *in vivo* mean heart rate from the groups (control animals: 307 ±

± 9 bpm, and animals with epilepsy: 346 ± 7 bpm). In contrast, we did not find differences during isolated *ex vivo* situation (control animals: 175 ± 7 bpm, and animals with epilepsy: 176 ± 6 bpm), suggesting a central nervous system modulation on the heart (such as the thalamic nucleus), which could explain sudden unexpected death in epilepsy. Quite interestingly and more recently, our group (Scorza et al., unpublished data) evaluated the heart rate (*in vivo* and isolated *ex vivo*) of rats with epilepsy before and after bilateral LP lesion. The results showed significant differences in the *in vivo* mean heart rate but, surprisingly, no differences in the heart rate could be observed in the isolated *ex vivo* situation. These observations seem to indicate a certain kind of specific thalamic modulation over the heart functioning, which could support our hypothesis of SUDEP due to heart failure as a consequence of thalamic dysfunction.

Neurocardiology has many dimensions [50], and we believe that the brain's effects on the heart are the most fascinating areas of research. To date, there is clear evidence suggesting that the cerebral mechanisms or the overactivity of the autonomic nervous system's sympathetic limb is the common phenomenon that links the major cardiovascular abnormalities seen in neurological disorders [50], including epilepsy. Thus, the presence of thalamic nuclei lesions in people with TLE could underlie some processes that culminate in SUDEP, and heart failure could play a significant role in this mechanism (Fig. 2).

Finally, we would like to emphasize that a clear relationship between TLE, thalamic dysfunction, heart failure and SUDEP still needs to be demonstrated both under experimental and human conditions. In the meantime, strategies such as taking a detailed cardiovascular history, looking for cardiovascular co-morbidity, evaluating cardiovascular risk factors and prior abnormal cardiac findings (electrocardiogram and echocardiogram) should be developed in an attempt to prevent SUDEP.

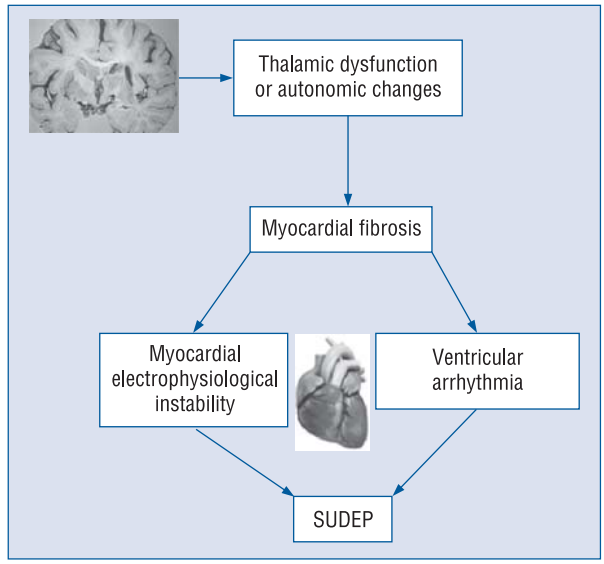

Figure 2. The hypothesis that cardiovascular abnormalities, and hence suden unexpected death in epilepsy (SUDEP), could be related to the occurrence of thalamic morphological or functional changes, at least in some cases, is proposed. Hippocampal atrophy and sclerosis are the most frequent abnormalities associated with temporal lobe epilepsy. However, brain structural changes are not confined solely to the hippocampus. Experimental and clinical data support an important role of the thalamic nuclei in the behavioural manifestations, initiation and propagation of seizures. Specific thalamic nucleus is directly related to the cardiovascular system. Thalamic dysfunction or autonomic changes can lead to myocardial fibrosis, which predisposes the development of ventricular arrhythmia or electrophysiological instability of the myocardium, increasing the risk of SUDEP.

Conclusions

SUDEP is the most important direct epilepsy-related cause of death and a number of its associated factors have been proposed. Mechanisms of SUDEP occurrence are still unclear and brain-heart connections may play an important role in the development of seizure-related and potentially fatal cardiac arrhythmias. The direct and indirect effects of some brain structures in the cardiac rhythm still need more elucidation. In the meantime, epileptologists should pay careful attention to the presence of cardiovascular associated diseases, especially in patients with associated potential SUDEP risk factors.

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References

1. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol, 2003; 16: 165–170.
2. Begley CE, Annegers JF, Lairson LB, Reynolds TF. Epilepsy incidence, prognosis, and use of medical care in Houston, Texas, and Rochester, Minnesota. Epilepsia 1998; 39 (suppl. 6): 222.
3. Annegers JF. Epidemiology of epilepsy. In: Wyllie E. The treatment of epilepsy: Principles and practice. 2nd Ed. Williams and Wilkins, Baltimore 1997: 165–172.

4. Yuen AW, Sander JW. Is omega-3 fatty acid deficiency a factor contributing to refractory seizures and SUDEP? A hypothesis. Seizure 2004; 13: 104–107.
5. Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psych, 2004; 75: 1376–1381.
6. Sander JW. Some aspects of prognosis in the epilepsies: A review. Epilepsia 1993; 34: 1007–1016.
7. Halatchev VN. Epidemiology of epilepsy: Recent achievements and future. Folia Medica (Plovdiv), 2000; 42: 17–22.
8. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet, 2006; 367: 1087–1100.
9. Dichter MA. Emerging insights into mechanisms of epilepsy: Implications for new antiepileptic drug development. Epilepsia, 1994; 35 (suppl. 4): S51–S57.
10. Dalby NO, Mody I. The process of epileptogenesis: A pathophysiological approach. Curr Opin Neurol, 2001; 14: 187–192.
11. Hirsch LJ, Hauser WA. Can sudden unexplained death in epilepsy be prevented? Lancet, 2004; 364: 2157–2158.
12. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: Current knowledge and future directions. Lancet Neurol, 2008; 7: 1021–1031.
13. Spratling WP. Prognosis. Epilepsy and its treatment. WB Saunders, Philadelphia 1904.
14. Nashef L. Sudden unexpected death in epilepsy: Terminology and definitions. Epilepsia 1997; 38: S6–S8.
15. Stollberger C, Finsterer J. Cardiorespiratory findings in sudden unexplained/unexpected death in epilepsy (SUDEP). Epilepsy Res, 2004; 59: 51–60.
16. Schuele SU, Widdess-Walsh P, Bermeo A, Lüders HO. Sudden unexplained death in epilepsy: The role of the heart. Cleve Clin J Med, 2007; 74: S121–S127.
17. So EL. What is known about the mechanisms underlying SUDEP? Epilepsia, 2008; 49 (suppl. 9): 93–98.
18. Scorza FA, de Albuquerque M, Arida RM, Cavalheiro EA. Sudden unexpected death in epilepsy: Are winter temperatures a new potential risk factor? Epilepsy Behav, 2007; 10: 509–510.
19. Baranchuk A, Nault MA, Morillo CA. The central nervous system and sudden cardiac death: What should we know? Cardiol J, 2009; 16: 105–112.
20. Singh RB, Kartik C, Otsuka K et al. Brain-heart connection and the risk of heart attack. Biomed Pharmacother, 2002; 56: S257–S265.
21. Scorza FA, Colugnati DB, Pansani AP, Sonoda EY, Arida RM, Cavalheiro EA. Preventing tomorrow's sudden cardiac death in epilepsy today: what should physicians know about this? Clinics, 2008; 63: 389–394.
22. Ryvlin P, Montavont A, Kahane P. Sudden unexpected death in epilepsy: From mechanisms to prevention. Curr Opin Neurol, 2006, 19: 194–199.
23. Bell GS, Sander JW. Sudden unexpected death in epilepsy. Risk factors, possible mechanisms and prevention: a reappraisal. Acta Neurol Taiwan, 2006; 15: 72–83.
24. Colugnati DB, Gomes PA, Arida RM et al. Analysis of cardiac parameters in animals with epilepsy: Possible cause of sudden death? Arq Neuropsiquiatr, 2005; 63: 1035–1041.
25. Lathers CM, Schraeder PL, Bungo MW. The mystery of sudden death: Mechanisms for risks. Epilepsy Behav, 2008; 12: 3–24.
26. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: Relation to sudden death in epilepsy. J Neurol Neurosurg Psych, 1996; 60: 297–300.
27. Nei M, Ho RT, Sperling MR. ECG abnormalities during partial seizures in refractory epilepsy. Epilepsia, 2000, 41: 542–548.
28. Drake ME, Reider CR, Kay A. Electrocardiography in epilepsy patients without cardiac symptoms. Seizure, 1993, 2: 63–65.
29. Tigaran S, Molgaard H, McClelland R, Dam M, Jaffe AS. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Neurology, 2003, 60: 492–495.
30. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: A review of incidence and risk factors. Epilepsia, 2005; 46: 54–61.
31. Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. Ann Neurol, 1989; 26: 195–203.
32. Devinsky O, Pacia S, Tatambhotla G. Bradycardia and asystole induced by partial seizures: A case report and literature review. Neurology, 1997; 48: 1712–1714.
33. Penfield W, Jasper H eds. Summary of clinical analysis and seizure patterns. In: Epilepsy and the functional anatomy of the human brain. LittleBrown, Boston 1954: 818–844.
34. Cheung RT, Hachinski V. The insula and cerebrogenic sudden death. Arch Neurol, 2000; 57: 1685–1688.
35. Seeck M, Zaim S, Chaves-Vischer V. Ictal bradycardia in ayoung child with focal cortical dysplasia in the right insular cortex. Eur J Paediatr Neurol, 2003; 7: 177–181.
36. Ryvlin P. Avoid falling into the depths of the insular trap. Epileptic Disord, 2006; 8: S37–S56.
37. Scorza FA, Sander JW, Cendes F, Arida RM, Cavalheiro EA. A possible role of the thalamus in some cases of sudden unexpected death in epilepsy. Epilepsia, 2007; 48: 1036–1037.
38. Jasper HH, Droogleever-Fortuyn J. Experimental studies on the functional anatomy of pett mal epilepsy. Res Publ Ass Nerv Ment Dis, 1947; 26: 272–298.
39. Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. Epilepsy Behav, 2002; 3: 219–231.
40. Macchi G, Bentivoglio M, Minciacchi D, Molinari M. Trends in the anatomical organization and functional significance of the mammalian thalamus. Ital J Neurol Sci, 1996; 17: 105––129.
41. Faull RLM, Mehler WR. Thalamus. In: Paxinos G ed. The rat nervous system. Vol. 1. Forebrain and midbrain. Academic Press Australia, Sydney 1985: 129–168.
42. Bonilha L, Kobayashi E, Rorden C, Cendes F, Li LM. Medial temporal lobe atrophy in patients with refractory temporal lobe epilepsy. J Neurol Neurosurg Psych, 2003; 74: 1627–1630.
43. Bonilha L, Kobayashi E, Cendes F, Min Li L. Protocol for volumetric segmentation of medial temporal structures using high--resolution 3-D magnetic resonance imaging. Hum Brain Mapp, 2004; 22: 145–154.
44. Bernasconi N, Bernasconi A, Caramanos Z, Andermann F, Dubeau F, Arnold DL. Morphometric MRI analysis of the parahippocampal region in temporal lobe epilepsy. Ann NY Acad Sci, 2000; 911: 495–500.
45. Bonilha L, Rorden C, Castellano G, Cendes F, Li LM. Voxel--based morphometry of the thalamus in patients with refractory medial temporal lobe epilepsy. Neuroimage, 2005; 25: 1016––1021.
46. Scorza FA, Arida RM, Priel M, Calderazzo L, Cavalheiro EA. The contribution of the lateral posterior and anteroventral thalamic nuclei on spontaneous recurrent seizures in the pilocarpine model of epilepsy. Arq Neuropsiquiatr, 2002; 60: 572–575.
47. Scorza FA, Sanabria ERG, Calderazzo L, Cavalheiro EA. Glucose utilization during interictal intervals in an epilepsy model induced by pilocarpine: A qualitative study. Epilepsia, 1998; 39: 1041–1045.
48. Boyko WJ, Galabru CK, McGeer EG, McGeer PL. Thalamic injections of kainic acid produce myocardial necrosis. Life Sci, 1979; 25: 87–98.
49. Colugnati DB, Gomes PA, Arida RM et al. Analysis of cardiac parameters in animals with epilepsy: Possible cause of sudden death? Arq Neuropsiquiatr, 2005; 63: 1035–1041.
50. Samuels MA. The brain-heart connection. Circulation, 2007; 116: 77–84.