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LETTER TO THE EDITORS

Late-onset cardiac arrhythmia associated with vagus nerve stimulation

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We report on a 13-year-old boy who first presented at the age of 5 years with refractory complex partial seizures (CPS) with and without secondary generalization. Despite a thorough workup no cause could be identified. After unsuccessful medical treatment attempts with 13 different antiepileptic drugs (AED) finally a vagus nerve stimulator (VNS; vagus nerve stimulation) was implanted in 2002 (NCP Type 101; Cyberonics, Houston, TX, USA). The intraoperative findings revealed no anatomic abnormalities and the lead test passed uneventfully. Eighteen months prior to the reported incident, seizure frequency was stable with three to five CPS per month under medication with phenobarbital (PB), felbamate (FBM), and zonisamide (ZNS). Due to former probably drug-related rickets the patient received also calcium and vitamin D supplementation with parameters of calcium metabolism stable within normal limits. VNS stimulation parameters were unchanged for the last years prior to the reported adverse effect (30 s on, 5 min off, 2.25 mA, frequency 20 Hz, pulse width 250 ms). Six and a half years after implantation a significant increase of seizure frequency was observed without apparent cause. Interventions with lorazepam, chloralhydrate, clobazam, and acetazolamide and a change of basic medication (i.e., stopping FBM) were unsuccessful. Suddenly an intermittent and self-terminating complete heart block with bradycardia occurring every 15–25 min lasting for 20–40 s over a time span of 2 h was recorded (Fig. 1). Several minutes later an asystole for 6 s was witnessed on the electrocardiogram (ECG) monitor. Assuming an influence of the VNS device, the stimulator was turned off and the bradyarrhythmia dissolved. Breakage of leads or abnormal placement of electrodes was ruled out by X-ray. A cardiological examination as well as laboratory workup did not reveal any abnormalities. Seizures were finally terminated with thiopental. Outpatient follow-up including close ECG monitoring did not show any further episodes of cardiac arrhythmias.

More than 50,000 VNS implantations have been performed worldwide. Large studies have reported both effectiveness and safety of the device. Despite the close proximity of VNS and centers controlling cardiovascular function initial studies in both animals and humans failed to demonstrate a relevant effect on cardiac function. Recent studies produced inconsistent results [7, 8, 11, 13, 15], mostly focusing on severe incidents associated with the intraoperative lead test during VNS implantation [1, 3, 5, 6, 14]. All patients made an uneventful recovery (Table 1). Only recently were the first two patients with late onset of cardiac arrhythmia, years after implantation, reported [2, 9]. In our patient an influence of the VNS is the most likely explanation, as cardiac arrhythmias subsided immediately following inactivation of VNS. However, since the incident took place during a phase of increased seizure frequency, and seizures (in particular status epilepticus) are well known to affect cardiac rhythm, it might be possible that these circumstances as well as changes in medication predisposed our patient to bradyarrhythmia. Most data for people with VNS compared with those with severe complex partial-onset epilepsy without the device failed to demonstrate an increased mortality rate, albeit encompassing less than 5 years after VNS implantation [4]. Considering the long time interval between the VNS implantation and the adverse event in our patient it might

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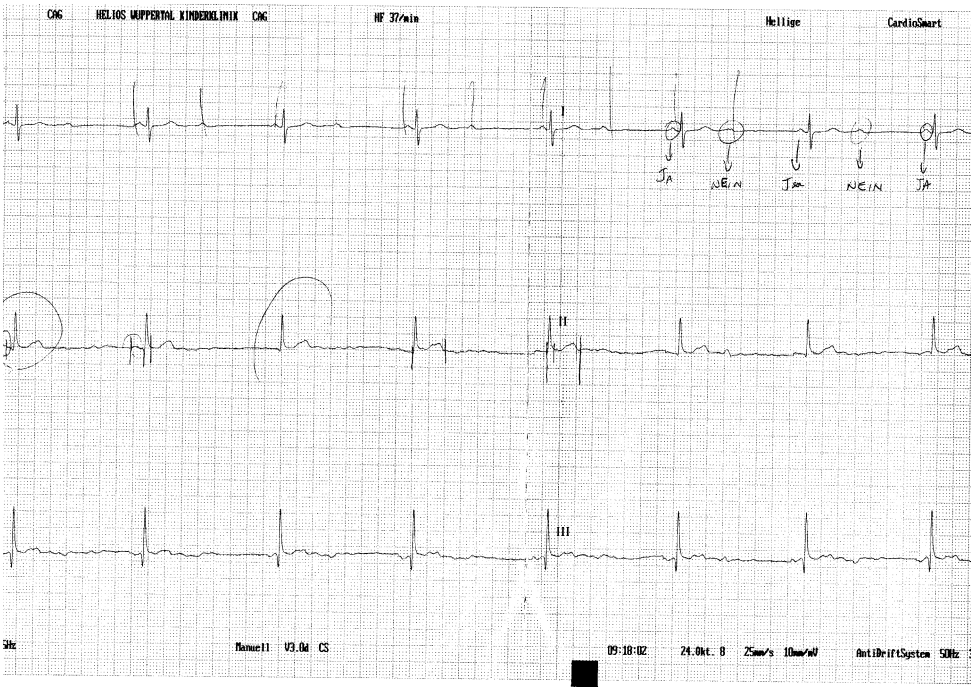

Fig. 1 ECG, showing intermittent heart block

Table 1 Patients with cardiac alterations

Reference	Age (years) gender	Type of epilepsy/ seizures	AED	Type of arrhythmia		Evaluation and additional evaluation
Ali et al. [1]	53 male	Atypical absences, generalized tonic-clonic	CBZ, VPA	15 s complete heart block with ventricular asystole	VNS removed	ECG, echocardiogram normal
Ali et al. [1]	40 male	CPS, myoclonic, generalized	CBZ, VPA	12 s ventricular asystole	VNS removed	ECG, 24-h telemetry echocardiogram normal
Ali et al. [1]	42 female	CPS	GBP, CLN	9 s ventricular asystole	VNS activated	First-degree heart block preoperative; diabetes and hypertension
Amark et al. [2]	17 male	CPS, secondary generalized	VPA, AZM, GBP	Sinusbradycardia, asystole, complete AV block	VNS removed	ECG with few supraventricular and ventricular extrasystoles
Ardesch et al. [5]	32 female	CPS	OXC, FBM	Bradycardia (43 and 25 bpm)	VNS activated	24-h ECG, echocardiogram normal; once tachycardia after using magnet to interrupt stimulation
Ardesch et al. [5]	52 male	Partial	PHT, TPM	Bradycardia (40 bpm)	VNS activated after 3 months	Later 24-h ECG and echocardiogram normal
Ardesch et al. [5]	59 female	Tonic-clonic	CBZ, VPA, CLN	Bradycardia (54 bpm)	VNS activated	
Asconapé et al. [6]	56 male	CPS	LTG, PRM	Bradycardia (30 bpm), transient asystole	VNS removed	ECG, 24-h telemetry echocardiogram normal
Koenig et al. [10]	8 female	CPS, atonic, tonic-clonic	OXC	Positive effect on heart rate variability		
Iriarte et al. [9]	47 female	Simple partial seizures, CPS	PGB, CLN, LEV	Bradycardia 8 s asystole	VNS stopped	

Table 1 continued

Reference	Age (years) gender	Type of epilepsy/ seizures	AED	Type of arrhythmia		Evaluation and additional evaluation
Srinivasan and Awasthi [12]	40 female	Partial seizures	Not specified	Atrial flutter and fibrillation	VNS stopped with later reactivation	Continuing paroxysmal runs of atrial flutter and fibrillation for 24 h after turning VNS off; no more arrhythmia after turning on the device at a later date
Tatum et al. [14]	38 female	CPS	LZP, PHT TGB	6 and 15 s asystole	VNS removed	ECG, 24-h telemetry echocardiogram normal
Tatum et al. [14]	57 male	Partial epilepsy	LTG PRM	Bradycardia 15 s asystole	VNS removed	ECG, 24-h telemetry echocardiogram normal
Tatum et al. [14]	38 male	Partial epilepsy	CBZ, VPA VGB	Bradycardia 10 s asystole	VNS removed	ECG, 24-h telemetry echocardiogram normal
Tatum et al. [14]	42 male	Partial epilepsy	TPM, FBM PHT, PB	45 s asystole	VNS activated	ECG, 24-h telemetry echocardiogram normal

CPS complex partial seizure, *AED* antiepileptic drug, *CBZ* carbamazepine, *VPA* valproic acid, *GBP* gabapentin, *CLN* clonazepam, *AZM* azetazolamide, *OXC* oxcarbazepine, *FBM* felbamate, *PHT* phenytoin, *TPM* topiramate, *LTG* lamotrigine, *PRM* primidone, *PGB* pregabaline, *LEV* levetirazetam, *LZP* lorazepam, *TGB* tiagabine, *VGB* vigabatrin, *PB* phenobarbital

be necessary to perform a long-term analysis on these side-effects.

The long time interval between implantation and onset of symptoms makes this a very insidious complication. This should sharpen the awareness of physicians involved in the care of patients with epilepsy and VNS for these complications. Special attention should be paid to patients with concomitant diseases or in critical situations.

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