Ictal asystole with reduced cardiac sympathetic function in new-onset symptomatic epilepsy

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SUMMARY
Introduction. So far, cardiac sympathetic dysfunction, demonstrated in pharmacoresistant epilepsy patients with ictal bradycardia or asystole by I-123 metaiodobenzylguanidine (I-123 MIBG) imaging has been attributed to repeated occurrence of seizure activity.
Aim. Discussion of the mechanisms of cardiac sympathetic dysfunction associated with ictal asystole under consideration of a case with new onset epilepsy.
Materials and methods. We describe the occurrence of a cardiac asystole during a complex-partial seizure in an antiepileptic-drug-naive patient with new-onset symptomatic epilepsy.
Results. MIBG imaging showed reduced tracer accumulation in cardiac sympathetic nerve endings in this patient with right parietotemporal glioblastoma.
Discussion and Conclusion. To our knowledge, this is the first report of impaired cardiac sympathetic function in new-onset symptomatic epilepsy without antiepileptic drug treatment. MIBG imaging should be considered in patients with ictal bradycardia or asystole.
Keywords: ictal asystole • MIBG imaging • symptomatic epilepsy • glioblastoma

INTRODUCTION
Involvement of the autonomic nervous system often occurs during epileptic seizures. Frequent autonomic symptoms include for example sweating, pupil dilatation or tachycardia. In contrast to the latter, ictal bradycardias or even asystoles are rare. In retrospective analyses of data from presurgical video-electroencephalography-monitoring, ictal asystoles of 5 to 60s duration were found in 0.27 to 0.59% of patients (Kerling et al., 2009; Rocamora et al., 2003; Schuele et al., 2007). Nevertheless, ictal bradycardias and asystoles are of relevance for the affected patients, since they usually go along with syncoles, often accompanied by falls and risk of injury. A higher risk of sudden unexpected death in epilepsy (SUDEP) in these patients has been widely discussed but could not be proven yet. The pathophysiology underlying ictal bradycardias is not entirely clear, however, a key role is attributed to an imbalance in the autonomic nerve system (Sforza et al.,

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In patients with long-lasting temporal lobe epilepsy (TLE), however, cardiac sympathetic denervation has been shown by means of I-123 metaiodobenzylguanidine (MIBG) imaging, a scintigraphic method using an analogue of norepinephrine, that is retained in sympathetic nerve endings. Among the investigated patients with TLE, the finding was significantly more pronounced in those experiencing asystoles with their seizures (Druschky et al., 2001; Kerling et al., 2009).

AIM
Case presentation and discussion of the mechanisms of cardiac sympathetic dysfunction associated with ictal asystole under consideration of a case with new-onset epilepsy.

MATERIAL AND METHOD
Here, we report on an antiepileptic-drug-naïve patient suffering ictal asystoles as the sole seizure manifestation of new-onset symptomatic epilepsy due to glioblastoma of the right parietotemporal lobe, in whom MIBG scanning demonstrated marked sympathetic denervation of the heart.

RESULTS
Case
A 71-year old male patient was admitted to our department with recurrent glioblastoma WHO °IV of the right parietotemporal lobe for brachytherapy. The tumour was diagnosed 11 months before by MRI and histopathological analysis after a hemianopsia to the left side had been found during a routine ophthalmological examination. First-line therapy had consisted of incomplete surgical resection with implantation of carmustine wafers and subsequent radiotherapy with concomitant and adjuvant temozolomide chemotherapy. The decision for implantation of iodine-125-seeds was made because of further progression of the tumour. Clinical neurological and neuropsychological examination revealed homonymous hemianopsia to the left, reduced alertness and mild to moderate executive dysfunction. There was no history of epileptic seizures in terms of overt clinical seizure manifestation. However, the patient reported on two events with loss of consciousness preceded by nausea and dizziness shortly before the diagnosis of tumour. Otherwise, medical history revealed no relevant diseases, especially no history of cardiovascular or Parkinson's disease; the patient was not taking any regular medication besides the above mentioned chemotherapeutics.
Sympathetic cardiac function in ictal asystole

During preoperative routine-EEG, the patient suddenly complained about a funny smell, then became unresponsive with staring followed by loss of consciousness with loose muscle tone and single bilateral asymmetric jerks before awakening. The patient was quickly reoriented and was amnestic for the episode. The EEG (fig. 1) initially showed continuous right frontotemporal delta-slowing maximal at F4 without epileptiform discharges, ECG showed sinus rhythm with 72 bpm. Subsequently, rhythmic right temporal theta-activity developed 10 s before clinical seizure manifestation which included bradycardia. The patient became asystolic 66 s after clinical seizure onset, cardiac activity reoccurred after 23 s. Flattening of the EEG lasted 26 s (fig. 1).

Subsequent cardiological examination including chest X-ray, 24 h Holter-ECG and transthoracal echocardiography was unremarkable. MIBG imaging revealed a low myocardial MIBG uptake (heart/mediastinum ratio 1.6 after 15 min and 1.8 after 4 hours post injection) reflecting a decreased post-ganglionic cardiac catecholamine uptake in idiopathic Parkinson’s disease (left: anterior view; right: posterior view).

**DISCUSSION**

Ictal asystole is a rare manifestation of seizures mostly of temporal origin (Rocamora et al., 2003; Schuele et al., 2007; Tenyi et al., 2017). The exact pathomechanisms underlying this seizure mediated cardiac bradyarrhythmia are unclear. However, in patients with temporal lobe epilepsy (TLE), cardiac sympathetic innervation has been shown to be compromised using MIBG imaging (Druschky et al., 2001; Kerling et al., 2009) a finding that is significantly more pronounced in those TLE patients exhibiting ictal asystoles (Kerling et al., 2009). According to the literature there are two hypotheses concerning the pathophysiological meaning of this finding: It has been proposed that enhanced sympathetic outflow from brain regions activated during seizure propagation leads to a compensatory down-regulation of sympathetic nerve endings (Druschky et al., 2001, Kerling et al., 2009). Also, an inherent disturbance of cardiac sympathetic innervation accompanying neuronal migration disorders in TLE patients has been discussed (v. Manitius-Robeck et al., 1998). However, caused, deficiency of cardiac sympathetic innervation probably limits counterregulation of vagal activation thus facilitating cardiac bradyarrhythmias.

In its clinical appearance, the case presented here is typical for ictal asystoles as depicted in the literature: the patient experiences an aura, in this case in the form of a smelling sensation, followed by a complex-par-
tial seizure with staring and unresponsiveness. Both the semiology and the ictal EEG (fig. 1) are suggestive for a temporal lobe seizure. He then loses consciousness due to cerebral hypoperfusion and subsequently myoclonic jerks before awakening as an expression of cerebral reperfusion (Duplyakov et al., 2014). MIBG scanning in our patient showed a low post-ganglionic sympathetic innervation in a comparable degree as described in the literature (Druschky et al., 2001; Kerling et al., 2009). In the aforementioned studies, however, patients with ictal asystole and pathological findings on MIBG imaging had been suffering from chronic pharmacoresistant epilepsy either of unknown etiology or due to long-lasting epileptogenic lesions such as hippocampal sclerosis or low grade tumours. In contrast, the patient reported here suffered from new-onset symptomatic epilepsy, which had not been treated with antiepileptic drugs yet. Contrary to our case report, Tenyi et al. (2017) found in their metaanalysis of 156 patients that the group of new onset ictal asystole patients (defined as occurrence of ictal asystole within a year) had a significant higher preponderance of female patients and patients with heart disease.

For temozolomide, which the patient had been taking in the course of radiochemotherapy, cardiac side effects have not been described. There is one patient reported by Druschky et al. (2001) who had been suffering from TLE due to hippocampal gliosis for only one year, but in contrast to our patient she had a high seizure frequency of 15/month and was taking carbamazepine 1200 mg daily, a drug that is known to potentially cause bradycardia and other cardiac arrhythmias. In the other 21 patients described by Druschky et al. (2001) – mean duration of epilepsy was 21.8 years, and 10 patients were taking carbamazepine. The finding of a compromised sympathetic innervation of the heart in a patient with a newly acquired epilepsy with ictal asystoles challenges both of the above mentioned hypotheses: neither compensatory downregulation of sympathetic nerve endings due to repeated, seizure-driven, enhanced cerebral sympathetic outflow nor combined malformations of the peripheral and central nervous system can explain the occurrence of ictal asystoles on the basis of post-ganglionic sympathetic denervation of the heart in this case. Furthermore, a medication side effect is excluded in this drug-naive patient. Interestingly, only 18% of the patients with new-onset ictal asystole in the cohort of Tenyi et al. (2017), were pretreated with AEDs. Also, this group had a significantly higher proportion of epileptogenic lesions in MRI, so that it could be speculated that in these acute symptomatic subgroups of patients ictal asystole is a marker of different pathological mechanism compared to the “typical”, long-lasting epilepsy patient, who are more prone to SUDEP.

CONCLUSION
Dysfunctional cardiac sympathetic innervation should also be considered in patients with sporadic seizure occurrence, with a recent seizure onset and without intake of drugs with potential cardiac side effects. For further discrimination of the pathomechanism of cardiac autonomic seizures, MIBG imaging can be helpful in patients with this seizure type.

CONFLICT OF INTERESTS
All authors have no conflict of interest: neither the authors nor the author’s institution have a financial or other relationship with other people or organizations that may have influenced the presented work.

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