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CASE STUDY

Ictal bradycardia in a young child with focal cortical dysplasia in the right insular cortex

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Summary We report on a three and a half year old child with episodic sinus bradycardia during habitual seizures and prolonged interictal discharges due to focal cortical dysplasia in the anterior 2/3 of the insula and the inferior frontal cortex. Seizure-induced bradycardia is rarely reported in children. Bradycardia is suspected to be related to sudden death, a rare complication of a chronic seizure disorder. Several well-documented cases in adult patients reveal a high incidence of temporal epilepsy, but MRI and PET studies in healthy subjects suggest a major role of the insular cortex, especially the right, in cardiac regulation. Our finding underlines the predominance of the right insula in cardiac control, which already seems to be present in children.

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Introduction

Sudden death is a rare fatal complication that may occur in patients with recurrent seizures. One prospective study estimated the annual incidence to be between 1/200 and 1/2000,¹ depending on the characteristics of the various patient groups. Young epileptic patients seem to be equally affected:

a frequency of death 8.8 times higher in epileptic children compared to a reference population has been reported.²

There is accumulating evidence, based on well-documented case reports with simultaneous EEG-EKG recordings and intensive monitoring, that a cardiac arrhythmia, notably sinus bradycardia leading to asystole, may be the major cause of sudden unexplained death in epilepsy (SUDEP).³ In a recent review on ictal bradycardia in 46 patients, all but one patient was an adult (range: 17-81 years).⁴ In a recent case report of a five-month child,⁵ severe bradycardia was suspected to be of epileptic origin;

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however, no simultaneous EEG was obtained and a 24-h-EEG on the following day was normal. Thus, an epileptic origin is less clear which might explain why the child died despite antiepileptic medication and pacemaker implantation. In this report we describe a three and a half year old child who experienced periods of relative bradycardia simultaneously in association with epileptogenic discharges in the right fronto-temporal cortex.

Case report

The patient is a three and a half year old girl, the first child of two siblings, who presented with her first seizures at the age of 4 months. Pregnancy and birth were unremarkable. The family history was also unremarkable except for a second degree cousin with an unknown epilepsy disorder during childhood. Early developmental milestones were slightly delayed (walked at 15 months, first word at 17 months).

During neurological examination, she was a calm and cooperative child, showing a right hand preference. Neurological status was normal. Motor and cognitive development was at the 24-month level (Bailey Scales of Infant Development).

A right fronto-temporal or centro-parietal focus was noted in several EEGs, and the first MRI a few weeks after the first seizures showed a lesion in the right frontal region suggesting focal cortical dysplasia (FCD).

Intensive monitoring of the patient revealed a markedly higher frequency of seizures than the 5–15 seizures per day initially reported. More than 30 seizures occurred during 4 days of continuous video-EEG and ECG monitoring, i.e. several seizures per hour, despite continuation of her polytherapy (150 mg phenytoin, 1000 mg vigabatrin, 5 mg lamotrigine, 100 mg topiramate; for 15 kg weight). Her seizures were clinically all of similar semiology. She first presented clonic movements of the lower eyelids, with right predominance, then myoclonic jerks of the left upper limb or hemibody, followed by an extension of all four limbs, grinding of teeth, facial flush, piloerection over both legs, sometimes with left-sided predominance. Postictally, an increased muscle tone of the left hemibody was found.

Investigation for possible surgery was subsequently performed because of the frequent and refractory nature of the seizures. The ictal EEG was characterized by a relative diffuse flattening of the background activity, followed by rhythmic sharp slow waves over right frontal areas, followed by a different morphology and somewhat faster rate over right anterior temporal areas. Of inter-

est, the heart rate slowed markedly during the time that the patient was displaying vegetative changes. The baseline sinus rate of 120–150 bpm/minutes was frequently observed to suddenly drop to 60 bpm for 3–4 seconds, between 10 and 20 seconds after seizure onset, and then returned quickly to baseline. Seventy five percent of the analyzed 26 seizures were associated with instances of this type of brief ictal bradycardia. Similar episodes of sinus bradycardia were found to be associated with bursts of subclinical epileptiform activity in the interictal ECG. The tracing was characterized by sharp slow waves over right frontal cortex at 2 Hz and/or a more rapid rhythm of 4–5 Hz over the right fronto-temporal cortex (Fig. 1). No independent left hemispheric or posterior epileptiform discharges were found although spread of ictal activity to contralateral temporal regions was noted.

A high-resolution MRI revealed abnormal cortex in the right anterior two-thirds of the insula, including also the right inferior frontal gyrus, and partially the middle frontal gyrus (Fig. 2). The presence of an additional cortical hypersignal in the FLAIR sequences was noted in the insula. A positron-emission tomography (PET) revealed a right fronto-basal hypometabolism, concordant with the lesion, as well as a discrete hypermetabolism in the insular cortex. Both the MRI and PET findings in the insula were interpreted as signs of major epileptogenic activity. A 13½ h (7.22 pm to 8.49 am next day) continuous ECG recording (Holter) revealed a baseline sinus rhythm with a mean rate of 103 bpm and periods of sustained sinus tachycardia, with mean rates of up to 132 minutes⁻¹ and a maximum rate of 156 minutes⁻¹ during wake hours. There were no significant pauses, however, during the Holter recording, no seizures occurred. The recording was interpreted as normal, and no further cardiac exams were carried out.

Surgery was carried out through a right fronto-temporal craniotomy. There were no abnormalities on inspection; however, the inferior frontal region was slightly indurated on palpation. The resection included the inferior frontal gyrus laterally and extended to the orbital surface of the frontal lobe; posteriorly, it included the frontal operculum as the anterior aspect of the insular cortex and tissue overlying it. The tissue was also indurated and had a yellowish appearance. The histopathology examination revealed severe cortical dysplasia. The resection was restricted to the gross pathology and limited by normal surrounding white matter as determined by palpation and appearance. Some indurated tissue was left in the depth of the subsular region.



Figure 1 Interictal EEG/ECG. 'ECG' indicates the significant deceleration of the heart rhythm from 120 to 60 bpm which was associated to the occurrence of sharp waves, rhythmic or semi-rhythmic at 1-2 Hz, with maximum over the right frontal region. Bottom: time-scale.

During the subsequent 8 months of follow-up, the patient experienced two seizures during an attempt to withdraw the phenytoin. She has remained seizure-free after phenytoin reintroduction and has shown some developmental progress. A post-operative MRI showed the complete resection of the dysplastic lesion in the frontal cortex and the anterior aspect of the insula lesion. In the middle part of the insula, a small region of abnormal cortex persisted but the additional hypersignal changes seen in the pre-operative exam disappeared, concordant with the hypothesis of secondary changes due to ongoing epileptogenic activity. A post-operative ambulatory continuous-ECG recording was also obtained. The 23-hour recording revealed a baseline sinus rhythm of 106 minutes^{-1} without any significant bradycardia and was interpreted as being normal.

Discussion

Ictal bradycardia is a rare finding of a chronic epileptic disorder compared to ictal tachycardia.⁶

In this child, the duration of the bradycardia was only for a few seconds and thus not associated with hemodynamic impairment. However, since the child was operated relatively soon after the diagnosis of pharmacoresistant epilepsy, we cannot exclude that the bradycardia may have ultimately become more significant with time if the seizure disorder had remained uncontrolled.

There has been considerable research about the underlying anatomical correlates of this phenomenon. Ictal cardiac rhythm changes are more often associated with temporal lobe epilepsy, as compared to seizures of extratemporal lobe origin.⁷ However, while a recent literature review found a moderate predominance of left-sided temporal foci in those cases where side of onset was documented,⁴ other reviews and studies suggest a right-sided focus lateralization with secondary implication of left temporal lobe structures.^{3,8}

Although these observations indicate temporal lobe structures as underlying anatomical correlates, it is most likely the adjacent insular cortex, which controls the cardiac rhythm. In our case, temporal cortex was unrevealing in the MRI whereas

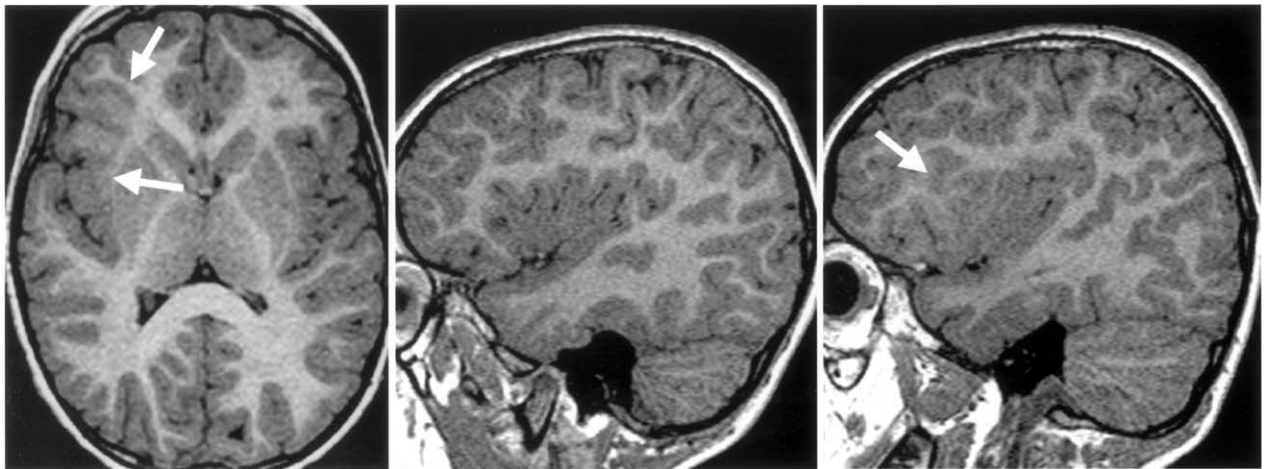


Figure 2 Left: Horizontal T1-MRI sequence (right hemisphere is on the left side of the picture). Middle: Sagittal T1-MRI sequence showing the left (normal) insula, Right: Sagittal T1-MRI sequence of the right insula. Note the dysplastic features of the anterior 2/3 of the insula and adjacent frontal cortex (→) in this three and a half year old epileptic child.

the anterior 2/3 of the insula showed dysplastic tissue. Perioperative stimulation of human insular cortex (in adult patients) has been described to result in heart rate changes with or without concurrent blood pressure variations.⁹ Stimulation of the left-sided insula resulted in bradycardia more often, but the changes were rather discrete. Other evidence, obtained in patients and healthy subjects, however speaks in favor of a major contribution of the right insula to cardiac regulation. An increased incidence of abnormal heart rate variability parameters and sudden death has been found most often in patients after right-sided strokes—if the insular cortex was involved.¹⁰ Moreover, in healthy subjects, the right insular cortex appears to be more associated with cardiac control than the left, as shown by fMRI¹¹ and PET¹² studies. These findings indicate a hemispheric lateralization of cerebral autonomic control in man with a more active role of the right insular cortex. This is supported by our observation, which also indicates that this lateralization is already present in children. In addition the insular cortex is also implicated in a variety of other vegetative functions, and interestingly in our patient the onset of bradycardia was synchronous with the appearance of facial flush and piloerection. Of interest, the concomitant activation of the insular cortex was described in 60% of patients with mesiotemporal epilepsy in a recent PET study.¹³

Phenytoin, which was part of our patient's antiepileptic medication, is known to have antiarrhythmic effects, but no significant bradycardia has been reported in long-term ECG monitoring studies of patients presenting with phenytoin

overdose.¹⁴ Moreover, phenytoin therapy would not explain the intermittent occurrence of the relative bradycardia episodes, although a synergistic effect of epileptogenic discharges and a modulation of the cardiac rhythm via the central nervous system by phenytoin cannot be excluded.¹⁵

Only prolonged simultaneous EEG-ECG recording permits the detection of such a complication, which, if significant, would necessitate the implantation of a pace-maker.⁸ In addition, it should be appreciated that risk of sudden death may persist after epilepsy surgery, as indicated by an elevated mortality risk in patients with right (as compared to left) mesial temporal epilepsy.¹⁶ Whether this is related to additional undetected epileptogenicity of the adjacent right insular cortex or not, remains to be addressed by prospective studies.

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