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Review / Derleme

Current View of Autonomic Findings During Epileptic Seizures

Epileptik Nöbetlerde Ortaya Çıkan Otonomik Belirti ve Bulgulara Güncel Bakış

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Summary

Autonomic findings during epileptic seizures frequently associate other ictal symptoms or may appear isolated. These changes are often overshadowed by other dramatic motor symptoms and not recognized. Cardiovascular system changes are thought to play a particular role in sudden unexplained death in epilepsy (SUDEP). In the literature, information about the features of peri-ictal autonomic symptoms and their lateralizing value are controversial. It is important to identify patients who are at high risk for SUDEP and plan early and appropriate medical treatment, as well as epilepsy surgery options to reduce mortality related with seizures. This paper will review the literature of the frequency of peri-ictal autonomic findings and their lateralizing and localizing information with didactic case examples. Furthermore, the relation between cardiac rhythm disorders, other electroclinical data, and risk of SUDEP will be evaluated.

Keywords: Epilepsy, peri-ictal autonomic findings, autonomic aura, SUDEP

Öz

Epileptik nöbetler sırasında ortaya çıkan otonomik bulgular sıklıkla diğer nöbet belirtilerine eşlik edebildiği gibi izole olarak da belirebilir. Bu bulgular diğer dramatik motor belirtilerin gölgesinde kaldıklarından az tanınmaktadır. Epilepsi hastalarında ortaya çıkan ani açıklanamayan ölümlerde (sudden unexplained death in epilepsy, SUDEP) otonomik sinir sisteminin, özellikle kardiyovasküler sistem üzerindeki etkisinin rol oynadığı düşünülmektedir. SUDEP için yüksek riskli hastaların belirlenmesi ve uygun hastalara erken dönemde kardiyak tedavi seçenekleri yanı sıra mümkünse epilepsi cerrahisi planlanması mortaliteyi azaltabilir. Literatürde peri-iktal otonomik bulguların özellikleri ve lateralizasyon değeriyle ilgili bilgiler tartışmalıdır. Bu derlemede epileptik nöbetlere eşlik eden otonomik belirtilerin sıklığı, lateralizan ve lokalizan değerleri literatür ve öğretici örnek olgular eşliğinde tartışılacak, epilepside ani ölüm riski, kardiyak ritim bozukluğu ve diğer elektroklinik veriler arasındaki ilişki değerlendirilecektir.

Anahtar Kelimeler: Epilepsi, peri-iktal otonom bulgular, otonomik aura, SUDEP

Introduction

Autonomic symptoms that occur during epileptic seizures often accompany other seizure symptoms and can also appear as isolated. Peri-ictal autonomic symptoms in adults are often seen in temporal lobe epilepsy (TLE) and may be associated with cardiovascular, respiratory, gastrointestinal, cutaneous, pupillary, genital, and urinary tract symptoms. Although autonomic changes are frequently seen during or after generalized tonic-clonic (GTC) seizures, these changes can also occur during focal seizures (1,2). Although autonomic changes are often observed during seizures, they mostly lag behind other dramatic motor signs. The assertion that peri-ictal autonomic changes may contribute to the mechanisms that cause sudden unexplained death in epilepsy (SUDEP) increases the importance of this issue (2). On the other hand, investigation of paroxysmal autonomic abnormalities, particularly peri-ictal tachycardia, which is frequently observed, would help in the development of algorithms for detection of seizures in advance, and to reduce mortality and morbidity in patients with epilepsy (3).

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Autonomic seizures are one of the major types of seizures of Panayiotopoulos syndrome, which affects approximately 13% of children with epilepsy aged between 3-6 years. During these seizures, which mostly occur following waking up, emesis, tachycardia, syncope-like symptoms, unilateral deviation of the eyes, progressive changes in consciousness, and termination with hemiconvulsions are seen. Almost half of the seizures last more than 30 minutes (autonomic status epilepticus) (4). It is believed that the seizure threshold of the central autonomic network is lower in children, and ictal discharges first activate autonomic centers with lower thresholds before other cortical centers, which causes focal cortical symptoms with higher thresholds (2). Other prominent epilepsies with autonomic symptoms are neonatal seizures, migratory focal epilepsy of infancy, Dravet syndrome, Rolandic seizures, TLE, and epilepsies with some specific genetic mutations in children and adults (5).

Autonomic seizures are defined as "An objectively documented and distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregularity functions" in the International League Against Epilepsy 2001 ictal semiology dictionary (6). Dependent on the affected organ systems, autonomic symptoms during seizures may be grouped as in Table 1 (2).

Peri-ictal Cardiac Changes

The effects of seizures on the cardiac system show a wide range of distribution such as variability in heart rate 'heart rate variability' (HRV), ictal sinus arrest, shortening of the QT interval, and atrial fibrillation (3). The most common cardiac changes during seizures are ictal tachycardia, ictal bradycardia, and changes in blood pressure (7). Although tachycardia may be associated with adaptive physiologic changes that follow emotional, motor or autonomic effects due to seizures, it can also be seen in the absence of such findings (3,7). Tachycardia can start before ictal changes on electroencephalographic (EEG) and during seizures (3,8). Pre-ictal tachycardia has been reported to be seen in 75% of seizures and monitored approximately 8-19 seconds before seizures (8,9). Ictal tachycardia is often seen in TLE and has been reported more in seizures with mesial temporal lobe onset (8,10). In some studies, ictal tachycardia has been reported to more frequently accompany right hemisphere seizures, but this finding has not been supported by other studies (8,10). It has been suggested that tachycardia may increase susceptibility to tachyarrhythmia and may pose a risk for sudden cardiac death and SUDEP both in the healthy population and in patients with epilepsy by leading to pathologic cardiac repolarization (11,12). It was reported that ictal maximum heart rate is higher in patients who died from SUDEP; increased heart rate is seen in seizures upon waking from sleep, and ictal cardiac repolarization and rhythm abnormalities are more frequent (13). In addition, antiepileptic drugs, especially carbamazepine and phenytoin, may also affect autonomic function and have proarrhythmic effects (7). The effect of beta-blockers for the prevention of SUDEP has been discussed by some authors (11). It has been suggested that heart rate reduction in patients with increased sympathetic tone may be a plausible approach for patients at risk of SUDEP (14).

Table 1. Autonomic symptoms during seizures relative to the affected organ systems	
Cardiovascular	Tachycardia, bradycardia, asystole, cardiac arrhythmia, arterial hypertension or hypotension
Gastrointestinal	Emesis (vomiting, belching or vomiting), epigastric aura, spitting, diarrhea, encopresis, "borborygmi"
Genitourinary and sexual	Urinary incontinence, genital sensation, sexual and reproductive automatism, erection, orgasm, ictal urinary urge
Respiratory	Hypopnea, apnea, hyperventilation, tachypnea, cough, neurogenic pulmonary edema, nocturnal acute laryngospasm
Vasomotor and pilomotor	Flushing, pallor, cyanosis, hyperhidrosis, piloerection, sweating, hypersalivation, lacrimation
Pupillary	Mydriasis, miosis
Thermoregulatory	Fever

On the other hand, ictal bradycardia is seen very rarely compared with tachycardia and it has been reported in less than 5% of seizures (8,15). Cardiac asystole is even rarer (16,17). In the majority of patients with ictal bradycardia, seizure foci have been localized to the temporal lobe (15,18). Though the information about lateralization is not clear, left hemisphere seizures have been observed to accompany ictal bradycardia more often (16,18). Some authors have reported that ictal bradycardia is not a reliable lateralizing finding and that it often accompanies bilateral hemispheric seizure activity (15). Other cardiac rhythm disorders reported during seizures are ST depression, atrial and ventricular premature beats, sinus arrest, atrioventricular block, and paroxysmal supraventricular tachycardia (19,20).

Along with the amygdala and hypothalamus, the anterior cingulate-, insular-, posterior orbitofrontal-, and prefrontal cortex affect the autonomic nervous system at the cortical level. The emergence of ictal activity in these structures or spread to these structures can lead to sympathetic and parasympathetic changes that affect the heart rate in patients with epilepsy (7). It was shown that metaiodobenzylguanidine (MIBG) uptake is reduced at myocardial sympathetic nerve terminals in patients with chronic TLE and this reduction has been suggested to be an indicator for reduced post-ganglionic sympathetic innervation (21). Decreased innervation may lead to hypersensitivity of cardiac beta-adrenergic receptors. Denervation-induced hypersensitivity may explain the positive chronotropic effect of sympathetic nervous system during seizures (22). In addition, increased sympathetic activity can cause secondary enlargement of the ventricular walls and lead to Takotsubo cardiomyopathy, which is reported in patients with epilepsy (23).

In a mortality study conducted in epilepsy monitoring units, 16 definite or probable, and 9 possible SUDEP cases were identified (24). In these cases, rapid breathing right after seizure (18-50 /min), followed by apnea, bradycardia, and generalized EEG suppression were seen, as in our patients. Some of these patients attracted attention because they were lying in the prone position. Hypoventilation during generalized seizures leads to oxygen decrease and respiratory acidosis. It has been suggested that the inability to increase the thoracic volume in the prone

position and the consequent inability to respire sufficiently could contribute to this condition (22,24). Careful analysis of peri-ictal cardiac changes and accompanying electrophysiologic features during video-EEG monitoring (VEM) and assessment of findings within cardiology departments can be very valuable in terms of early detection of patients with SUDEP risk and must not be neglected.

In our study on epilepsy patients with seizures with peri-ictal autonomic findings, it was observed that significant ECG changes accompanied seizures in 8% of patients (4 patients). Sinus arrest after secondary generalized seizure followed by bradyarrhythmia and "rebound" tachycardia was observed in two patients, both of whom had generalized EEG suppression during bradyarrhythmia (Figure 1). In addition, severe supraventricular tachycardia in was noted in one patient (Figure 2a, 2b) and premature ventricular complexes in one other (1).

Peri-ictal Respiratory Changes

Ictal respiratory changes often impair ventilation accompany GTC seizures. Ictal respiratory changes and ictal oxygen desaturation of below 90% have been reported in about 1/3 of focal seizures (25). Saturation falls below 70% in 3.4% of patients. There are insufficient data on the mechanisms that underlie ictal hypoxia and hypercapnia. It was reported that ictal hypoxia accompanies hypercapnia, is more frequently seen in temporal lobe onset and right hemisphere seizures, and that seizure duration and spread to contralateral hemisphere deepen hypoxia (25,26). It has also been proposed that central hypoventilation occurs due to direct effects of seizures on the respiratory center in the brain stem, which leads to ictal hypoxia and hypercapnia (2).

Ictal hypoventilation, central apnea, neurogenic pulmonary edema, and asphyxia are considered some of the possible mechanisms of SUDEP (25,27). It is recommended that patients with epilepsy should be monitored with oximetry in monitoring units. Early intervention by nurses during the peri-ictal period has been reported to shorten the period of respiratory dysfunction and reduce the risk of SUDEP (28).

Cough may occur during the ictal- or post-ictal period. Although post-ictal cough seems to be a feature of TLE in some studies, it was reported not lateralize or localize in other studies. Post-ictal cough may occur as a response to increased respiratory secretions but can also as a result of direct activation of central autonomic pathways (29,30). In different studies, the incidence of peri-ictal cough in patients with TLE was reported as 5-24%. In our study, peri-ictal cough was observed in 4 (8%) of 48 patients with recorded seizures. Cough was post-ictal in 3 patients and ictal in 1 patient. Four patients were classified as having TLE. Three patients had hippocampal sclerosis in etiology. Cough accompanied left frontotemporal region onset seizures in 3 patients and right frontotemporal region onset seizure in 1 patient. In addition to cough, other autonomic symptoms such as nausea and spitting accompanied in 1 patient (1).

Post-ictal nose wiping has been reported in approximately 50% of patients with TLE, seizure onset is in the ipsilateral side in about 85-92% of patients (31). They are less common in patients with extratemporal onset seizures and we reported that they also accompany absence seizures (32,33). Activation of the central autonomic network, particularly the amygdala, is thought to lead to nasal secretion. Ictal nose wiping was observed in a case with depth electrode monitoring only when ictal activity occurred in the amygdala (34). Use of the ipsilateral hand may be due to mild post-ictal contralateral paresis or neglect (31,34).

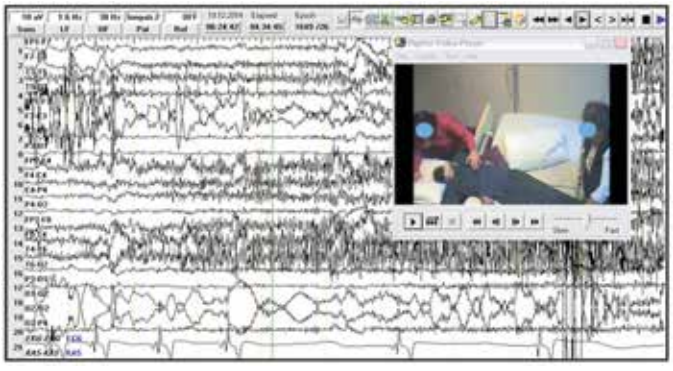

Figure 1. Sinus arrest accompanying generalized EEG suppression after generalized seizures

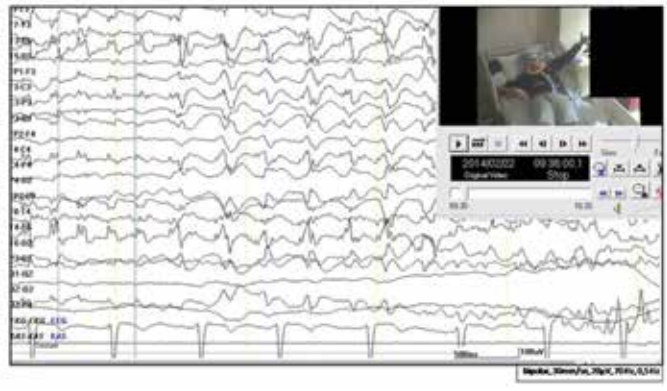

Figure 2a. Supraventricular tachycardia following ictal bradycardia in a patient with Rasmussen's encephalitis

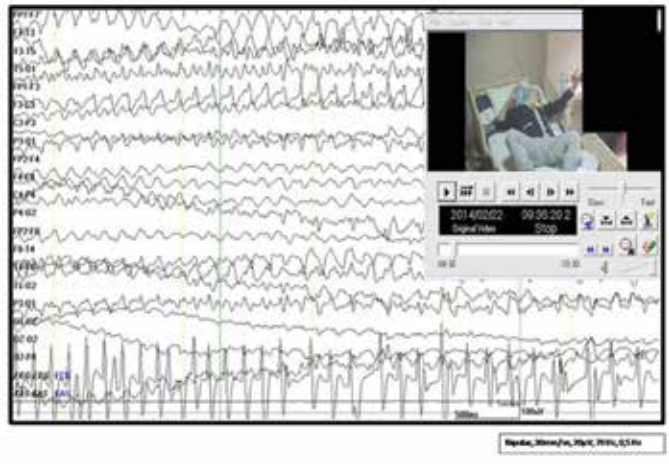

Figure 2b. Supraventricular tachycardia following ictal bradycardia in a patient with Rasmussen's encephalitis

Epigastric Aura, Peri-ictal Nausea, and Vomiting

Epigastric aura is the most common visceral finding in adults with epilepsy. It is more common in TLE compared with extratemporal lobe epilepsy. It is more frequent in mesial TLE than in neocortical TLE. If epigastric aura is followed by oral or manual automatisms, seizure is most likely to be localized to the temporal lobe. A lateralizing value has not been shown (35). An epigastric sensation often starts at the midline of the epigastrium and stomach, remains localized or rises up to thorax, chin or face (36).

Janszky et al. (29) reported abdominal aura in 62% of patients with TLE. Ictal vomiting and retching (7-10%) are very rare findings of seizures. Ictal nausea, vomiting and retching symptoms have been lateralized to non-dominant temporal lobes in many studies (37). In a few rare cases, similar to our three cases, ictal vomiting has also been reported in left (dominant) temporal onset seizures (1,38,39,40). Functional hemispheric asymmetry in the control of gastrointestinal motility has been proposed as an explanation for lateralization to the non-dominant hemisphere (36). The complex cortical network responsible for the formation of ictal vomiting was suggested to consist of medial and lateral parts of the temporal lobe, particularly the lateral-superior temporal cortex, and insula and occipital lobes (37).

Although rare in adult patients with epilepsy, ictal vomiting often accompanies benign childhood epilepsy with occipital spikes and photosensitive occipital lobe epilepsy (41). Although ictal vomiting in adults is associated with temporal lobe epileptic activity, multifocal epileptic discharges are more frequently seen in the occipital of children with Panayiotopoulos syndrome; ictal onset may be in the anterior or posterior areas (42,43). According to another view, epileptic cortical findings and vomiting are age-related, neurotransmitter-mediated processes and they occurdue to excitation of the vomiting center in the brain stem and cerebral cortex by sleep (as in Panayiotopoulos syndrome) or external stimuli (as in photosensitive occipital lobe epilepsy) (41,43).

In our study, peri-ictal nausea and retching were seen in 9 (18%) of seizure-recorded patients (9). When patients with no ictal monitoring and their histories were also included, nausea and retching with accompanying epigastric aura were present in 41% of the whole group. Right temporal lobe onset seizures were noted in 5 (55%) of our seizure-recorded patients with ictal nausea and retching, and left temporal lobe onset seizures in 4 (45%) right-handed patients (Figure 3). In contrast to most studies that lateralize ictal nausea and associate the non-dominant temporal lobe with retching and vomiting, ictal nausea and retching symptoms were not lateralized to any hemisphere in our patient group and the lateralizing value of these findings were thought to be suspicious (1).

Peri-ictal Spitting

Most studies have indicated that peri-ictal spitting has non-dominant temporal lobe onset seizures (44,45). Left (dominant) temporal lobe onset seizures accompanied by ictal spitting have also been reported by different authors (29,46,47). The incidence of peri-ictal spitting in TLE was reported to range between 0.3 and 2.2% (29,30,47). As most of the patients in the literature do not describe ictal gustatory hallucinations, ictal spitting can be accepted as a pure motor automatism such as chewing and swallowing movements, rather than a symptom in response to gustatory aura (36). Structures associated with autonomic functions are not thought to play a role in ictal spitting because ictal spitting is not usually seen with symptoms such ictal vomiting, coughing or fear. Park et al. (48) showed that ictal spitting emerged immediately after epileptic activity spread to the right hippocampus and amygdala in an intracranial EEG of a patient with left temporal lobe onset seizure and left hemisphere dominance. Right hemisphere lateralization of ictal spitting has been suggested to be associated with functional disorders of regions that control emotional behavior in non-dominant hemisphere makes patients spit aggressively at other people (45). Epileptic activity in extratemporal lobe onset seizures may spread to limbic structures through mesial occipital, parietal, and cingulate areas (45).

Peri-ictal Water Drinking

Peri-ictal water drinking has frequently been reported in the non-dominant temporal lobe seizures (30,49). In some studies, its lateralizing value could not be demonstrated (29,50). It has been stated that the fast spread of epileptic activity to the contralateral hemisphere makes it difficult to decide which temporal lobe leads to water drinking behavior (50). In our study, peri-ictal water drinking was observed in 8% of patients (4 patients) with recorded seizures and in 16% (10 patients) of the whole group when considered together with their histories (1). In other studies, this finding has been reported in 7-15% of patients with refractory epilepsy (29,30,49,50). In our study, peri-ictal water drinking was noted to be more frequent in TLE and although insignificant, in non-dominant hemisphere seizures (Figure 4) (1). Trinka et al. (49) argued that through pathways between mesial temporal structures and the hypothalamus spread of mesial temporal epileptic activity, caused thirst and water-seeking behavior and that lateralizing features of peri-ictal water drinking was associated with asymmetric representation of the central autonomic network, which is associated with fluid control and thirst. Musilova et al. (30) alternatively stated that patients with non-dominant TLE respond to external stimuli more often than patients with dominant TLE during seizures and that they may react with drink-seeking behavior when they feel a dry mouth and are thirsty.

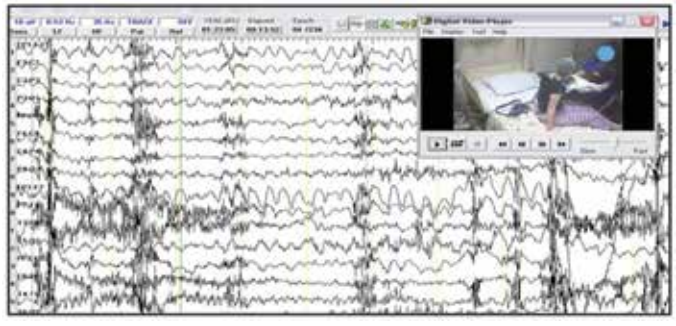

Figure 3. Ictal activity with 4-5 Hz frequency and prominent rhythmic theta waves was noted in left frontotemporal region during nausea and retching in a patient with left hippocampal sclerosis

Peri-ictal Hyperthermia

Hyperthermia can occur in rare cases of generalized or focal or non-convulsive seizures (51,52). Peri-ictal hyperthermia has no lateralizing or localizing value. It has been suggested that epileptic activity, which especially occurs in mesial temporal structures, could affect thermoregulatory centers by spreading to the pre-optic area in the hypothalamus. The vagal nerve nucleus (nucleus tractus solitarius) may be affected during seizures or seizures may give rise to pyrogens in many regions of the brain such as the neocortex, amygdala, and hippocampus (52). In our series, high fever was detected in 2 patients in both history and in the pre- and post-ictal period during VEM. Fever fell within 12 hours in these patients. No infection markers were detected in surveys that were performed to rule out infection. In 1 patient without recorded seizures, it was learned from the patient's history that recurrent high fever was confirmed by measurements after seizure. Two patients had bilateral hippocampal sclerosis due to TLE and 1 patient was diagnosed as having frontal lobe epilepsy due to bilateral frontal encephalomalacic regions that resulted from meningioma surgery (Figure 5) (1).

Ictal Hypersalivation

In our study, 89% of patients with peri-ictal hypersalivation were observed to have non-dominant hemisphere onset seizures. Sixty-six percent of patients are diagnosed with TLE. Although some authors likewise reported more frequent hypersalivation with non-dominant hemisphere onset seizures, some authors have argued that hypersalivation has no lateralizing value (29,53). Increased hypersalivation and saliva flow during seizures in benign childhood epilepsy with centrotemporal spikes is a common finding. Increased saliva has been suggested to be associated with hyperexcitability in opercular areas (54). In studies with intracranial depth electrodes, peri-rolandic opercular area onset seizures have been indicated to cause hypersalivation and orofacial and pharyngeal symptomatology (55,56). Different anatomic structures have been reported to cause ictal hypersalivation in different case reports and studies. These are medial temporal lobe structures, the orbitofrontal and dorsolateral frontal cortex, postcentral gyrus, and parietal operculum (53,54,55,56).

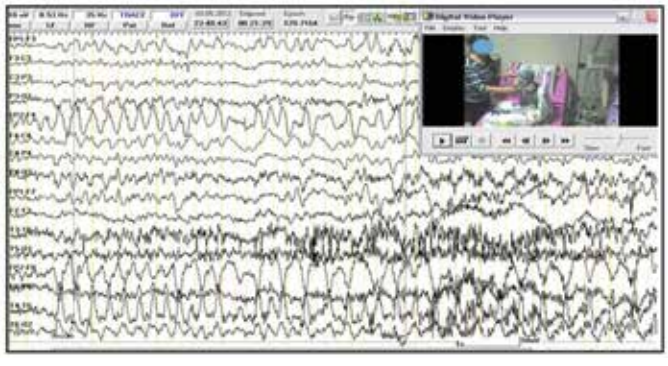

Figure 4. Prominent rhythmic ictal activity with 4 Hz frequency was observed in right frontotemporal region during water drinking in a patient with right hippocampal sclerosis

Ictal Urinary Urge and Urination

Urinary incontinence frequently accompanies generalized GTC seizures leading to full unconsciousness. Intravesical bladder volume increases in the tonic phase of generalized seizures and progressively decreases in the clonic phase; enuresis occurs with urinary sphincter relaxation if the bladder is full during seizures (57). Enuresis may also accompany absence seizures. Disinhibition of subcortical centers, which control the micturition reflex, is thought to cause an increase in intravesical pressure and enuresis (58). Ictal urinary urge is rarely seen in focal seizures and its prevalence varies between 0.4% and 3% in TLE (29,59,60). In previous studies, ictal urinary urge has been reported in non-dominant hemisphere, especially in temporal lobe onset seizures (59,60). In another study with few cases, ictal urinary urge has been reported not to be important in lateralization of seizure activity (29). Detection of hyperperfusion in insula and superior temporal gyrus on single-photon emission computed tomography (SPECT) in two patients indicated the role of the insular cortex in the emergence of these symptoms (59). It has been suggested that epileptic activity in the insular cortex causes a sensation of bladder fullness and the ictal urinary urge (36). However, ictal urinary urge and enuresis may occur as a result of spread of epileptic activity to the right inferior frontal cortex, which plays an important role in the suprapontine control of bladder (36).

Genital Automatism

Genital automatisms are defined as repetitive touching to the genital area during or after seizure. It has been reported to accompany temporal lobe seizures (61,62). In other studies, it was stated that it has no lateralizing and localizing features alone, and that it can be localized to the non-dominant temporal lobe in the presence of peri-ictal urinary urge and to the ipsilateral temporal lobe in the presence of unilateral hand automatisms (63). Sexual

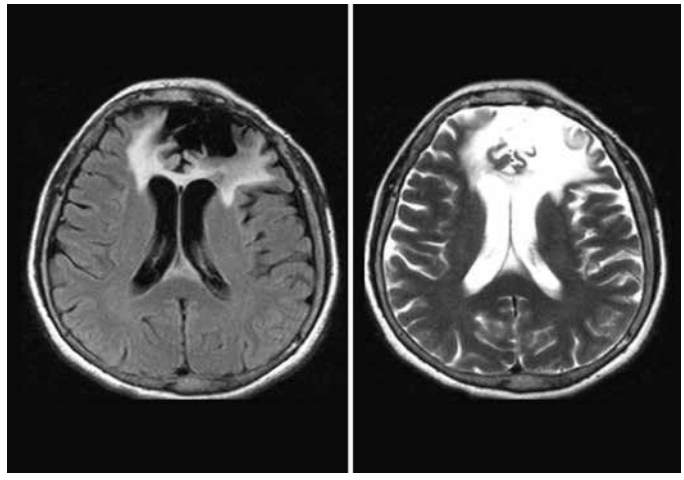

Figure 5. Encephalomalacic regions in the left frontal lobe and medial part of the right frontal lobe secondary to surgery. Diffuse hyperintense gliotic region on T2 and fluid attenuation inversion recovery sequences. Ictal hyperthermia was found in the patient with bilateral lateral ventricle enlargement

hypermotor pelvic and truncal movements can indicate frontal lobe seizures unlike genital automatism (61,64). In patients with genital automatisms together with hypermotor activities, such as fast pelvic movements, kicking, and shaking, seizures emerging from medial or orbital frontal regions have also been recorded in recordings with depth electrodes (65). Differentiating hypermotor sexual automatisms from recurrent genital automatisms has been indicated to be important for differentiation of temporal and frontal lobe seizures (61). Although genital automatism has been reported in patients with focal seizures in most studies, genital automatism can also be seen in patients with generalized epilepsy (63). The possible role of the temporal lobe in the formation of sexual behavior was noted in monkeys and humans that showed excessive masturbation behavior and hypersexuality following bilateral temporal lobectomy (64,66). Genital automatism can also be a nonspecific reaction in response to stimuli such as peri-ictal sensation of urination (Figure 6). In our study, obvious genital automatism was observed in 5 (10%) patients with recorded seizures. Four of these patients were diagnosed as having TLE (hippocampal sclerosis). Three patients had left- and 2 patients had right hemisphere onset seizures. None of the patients had sexual aura. The hand with which genital automatism was implemented was on the same side as the initial ictal EEG in all patients (1).

Conclusion

Autonomic symptoms that occur during epileptic seizures may accompany other seizure symptoms or occur alone. Some autonomic symptoms may provide lateralizing or localizing information that indicate the onset of seizures, but reliability is not usually one hundred percent. As cardiovascular or respiratory autonomic symptoms may be related to the mechanisms that underlie SUDEP, these mostly-neglected findings should be well researched. Careful analysis and correct evaluation of autonomic symptoms that occur during seizures is important in terms of understanding the risk of SUDEP, involvement of neuronal networks, and results and spread pattern of ictal activity.

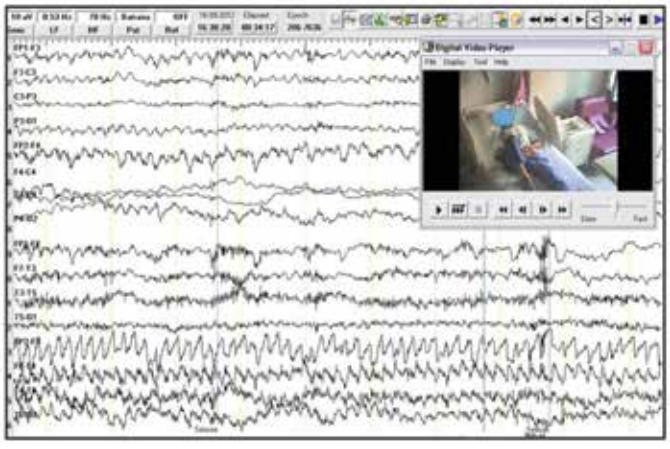

Figure 6. Ictal activity with 7-8 Hz frequency and rhythmic sharp waves was noted in the right frontotemporal region during right-hand genital automatism in a patient with right hippocampal sclerosis

Authorship Contributions

Concept: Leyla Baysal Kıraç, Betül Baykan, Design: Leyla Baysal Kıraç, Betül Baykan, Data Collection or Processing: Leyla Baysal Kıraç, Analysis or Interpretation: Leyla Baysal Kıraç, Betül Baykan, Literature Search: Leyla Baysal Kıraç, Writing: Leyla Baysal Kıraç, Peer-review: Externally peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared no financial support.

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