Research Article

DOI: 10.5152/NSN.2019.10702

Autonomic dysfunction during the interictal period: an electrophysiologic study

Arife Çimen Atalar[1], Feray Karaali Savrun[2], Seher Naz Yeni[2]

[1]Clinic of Neurology, İstanbul Training and Research Hospital, İstanbul, Turkey
[2]Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey

Abstract

Objective: Autonomic nervous system dysfunction during the interictal period of epileptic seizures is still poorly understood. We assessed sympathetic and parasympathetic functions during the interictal period using sympathetic skin response (SSR) and R-R interval variability (RR-IV) methods in patients with epilepsy.

Methods: We questioned the presence of autonomic symptoms in 50 patients with epilepsy and 42 healthy controls. We also measured SSR and RR-IV percentage (RR-IV%) at rest, deep inspiration, and during the Valsalva maneuver. Orthostatic hypotension (OH) was also evaluated.

Results: Of the 50 patients with epilepsy, 21 patients had temporal lobe epilepsy (TLE) and 29 had extratemporal lobe epilepsy. Autonomic symptoms (orthostatic intolerance, gastromotor, pupillomotor, vasomotor, secretomotor symptoms) and OH were significantly more common in patients with TLE ($p<0.05$). The SSR amplitude was higher in patients than in controls ($p<0.05$) and the RR-IV% values at rest, during deep inspiration, and during the Valsalva maneuver were significantly lower in the patient group than in the control group ($p<0.01$ for each). As a result, autonomic symptoms were more common in patients with TLE comparing with extratemporal epilepsy in the interictal period. RR-IV% values were lower than in the control group at rest, deep inspiration, and the Valsalva maneuver in patients with epilepsy. Sympathetic skin response amplitude is higher in patients with generalized seizures, reflecting increased sympathetic responsiveness in the interictal period.

Conclusion: Our study demonstrated clinical and electrophysiologic findings supporting autonomic system dysfunction in patients with epilepsy during the interictal period.

Keywords: Autonomic system dysfunction, extratemporal lobe, parasympathetic system, sympathetic skin response, temporal lobe

INTRODUCTION

Partial and generalized epilepsies can alter autonomic functions in the ictal, interictal, and postictal periods (1). Partial epilepsies, especially temporal lobe seizures, may often manifest with significant and noticeable alterations in autonomic nervous system (ANS) functions (1). Recently, clinical studies have shown that heart rate and conduction abnormalities in the ictal period may play a role in the pathogenesis of sudden unexpected deaths in epilepsy (SUDEP), especially in young patients (1, 2). Seizures typically trigger sympathetic system activity and lead to an increase in heart rate and blood pressure. Sometimes, parasympathetic activation or sympathetic inhibition may accompany sympathetic overactivation.

The most practical and reproducible electrophysiologic methods that evaluate autonomic functions are sympathetic skin response (SSR) and R-R interval variability (RR-IV). Sympathetic skin response and RR-IV are reflectors of sympathetic and parasympathetic system functions, respectively. Sympathetic skin response measures the sympathetic cholinergic sudomotor function of the sympathetic nervous system by means of electrodermal activity (3). The electrodermal activity reflects the variability of skin resistance in response to electrical transmission. The source of this electric potential obtained via the skin is thought to originate from the dermal sweat glands and the epidermis (4).

You may cite this article as: Çimen Atalar A, Karaali Savrun F, Yeni SN. Autonomic dysfunction during the interictal period: an electrophysiologic study. Neurol Sci Neurophysiol 2019; 36(1): 9-15.

Corresponding Author: Arife Çimen Atalar **E-mail:** cimenatalar@yahoo.com.tr **Submitted:** 7 July 2018 **Accepted:** 19 December 2018

R-R interval variability is based on variability of the heart rate depending on respiration. Physiologically, the heart rate increases during inspiration and decreases during expiration due to the vagal innervation of the heart. This may be influenced by many factors: it decreases with age, it increases as respiration slows down, and it reaches its maximum at 5 to 6 inhalations and exhalations per minute.

In this study, we aimed to investigate the alterations of autonomic functions during the interictal period of epilepsy using SSR and RR-IV.

METHODS

Patient Selection

Our study included 50 patients, aged between 18 and 70 years, who were diagnosed as having epilepsy in accordance with the criteria of the International League against Epilepsy. The patients were admitted to the epilepsy outpatient clinic of neurology between 2015 and 2017. Forty-two age and sex-matched healthy individuals were included as the controls. The patient group was divided into two subgroups as temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ELE), according to their clinical semiology, electroencephalography, and neuroimaging findings. The ELE group was further subdivided into subgroups according to the site of origin of the seizure: frontal lobe, parietal lobe, occipital lobe, or generalized epilepsies. Subjects with the following conditions were excluded from the study: those taking medications that could affect ANS functions such as antihypertensive drugs or antiepileptic medications (e.g., carbamazepine, valproic acid and diphenylhydantoin), with a history of meningitis or head trauma, history of a cardiac disease (e.g., arrhythmias, heart block, or pacemakers), diabetes mellitus, polyneuropathies, multiple sclerosis, Parkinson's disease or other diagnoses of similar neurodegenerative disorders that could affect ANS functions. The control group was recruited from healthy medical students and staff of our faculty.

Our study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine Ethics Committee (Date 08.06.2009, Decision number: 16988), and written informed consent was obtained from all participants.

Patient Examinations

After detailed neurologic examinations, all participants were interviewed about the presence of the most common autonomic symptoms using a detailed questionnaire (COMPASS-31) (5). Measurements for evaluating orthostatic hypotension (OH) and electrophysiologic diagnostic tests (EPTs) were performed. The EPTs were conducted in a semi-darkened silent room, between 09:00 A.M. and 13.00 P.M. Room temperature was maintained between 22 and 24°C and the skin temperature of patients was at least 35°C while performing the EPT. A Neuropack eight-channel device (Nihon Kohden Corporation, Tokyo, Japan) was used for the EPT. Measurements were taken in a resting position and at least 4 hours after cessation of the consumption of nicotine and caffeine-containing substances such as cigarettes, tea, and coffee.

Orthostatic Hypotension Evaluation

We performed an orthostatic test for each subject. Blood pressures (using an Omron M3 Comfort sphygmomanometer, HEM-713-E, Kyoto, Japan) and heart rates of each subject were measured after a resting period of 30 minutes in the supine position (initial measurement), and repeated at the third minute of the standing position (second measurement). We defined OH as a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure 10 mmHg, and an increase of pulse rate by ≥5 /min at the third minute of the standing position (6).

R-R Interval Variability

The test for RR-IV was performed in a quiet room, while participants rested in the supine position. The superficial Ag/AgCl electrodes were fixed to the anterior chest area at the fourth and fifth intercostal space. The earth electrode was placed on the midline of the sternum. The trigger sensitivity and sweep speed were adjusted in the oscilloscope display using the triggering mode and delay line to display the QRS complexes on the screen. The first complex is assumed as the triggering potential, the variation in timing of the second complex is accepted as the variation in the RR interval. Three separate measurements were taken: at rest in the 1st minute of normal breathing, during deep inspiration (at a frequency of 6 breaths/min with equal inspiratory and expiratory cycles, each cycle of 5 seconds), and during the Valsalva maneuver (a forced expiration against a closed glottis after a deep inspiration for 15 seconds).

The electromyography device was set to 200 mV for sensitivity, the bandpass was 1-20 Hz, and 0.5 seconds for the scan speed. The RR-IV percentage (RR-IV%) was calculated using the following formula and results were recorded:

RR-IV% = (the longest RR - the shortest RR) × 100/mean of RR values (the difference between the shortest and the longest RR intervals during 1 min, given in percentage of the mean of all maximal and minimal peaks).

Sympathetic Skin Responses (SSRs)

The active Ag/AgCl electrode was placed into the palm and the reference electrode was placed onto the dorsum of the subject's hand. The earth electrode was placed in the midline of the frontal region of the head. The device was set to between 0.5 and 2 mV for sensitivity, bandpass 0.1-1000 Hz, and a 1 second scan speed. An electrical current of 12 mA was applied for 0.1 milliseconds to the midline nerve trace at the level of the contralateral wrist. Stimuli were applied unex-

pectedly and at irregular time periods to prevent a possible habituation. The SSR latency (the time required to reach the initiation of the first deflection of the wave in milliseconds) and the SSR amplitude (the peak-to-peak distance of the obtained wave in mV) were recorded.

Statistical Analysis

Data analysis was performed using the IBM Statistical Package for the Social Sciences Statistics for Windows, Version 22.0 (SPSS IBM Corp.; Armonk, NY, USA) software package. Data normality was evaluated using the Shapiro-Wilk test. We used descriptive statistical methods (mean, standard deviation, and frequency), Student's t-test for data with normal distribution, and the Mann-Whitney U test for data with non-normal distribution for the two group comparisons. We used Yates's continuity adjustment to compare qualitative data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the patient group, 21 patients had TLE and 29 patients had ELE. There was no significant difference between the patient and control groups in terms of age (p=0.085) or sex (p=0.188). The mean age of the patient and control groups was 36.78±13.01 and 41.40±12.31 years, respectively. The COMPASS-31 scores were 22.77±8.2 and 13.14±9.36 for the patient group and control group, respectively (p<0.01). The distribution of seizure types and the most common autonomic symptoms are presented in Table 1.

Table 1. Distribution of seizure types and autonomic symptoms in the patient group

	Number (%) of subjects
Seizure Types	
Frontal	11 (22)
Generalized	12 (24)
Occipital	4 (8)
Parietal	2 (4)
Temporal	21 (42)
Autonomic Symptoms and Signs	
Orthostatic intolerance	18 (36)
Secretomotor	26 (52)
Urinary	19 (38)
Gastrointestinal	18 (36)
Vasomotor	18 (36)
Pupillomotor	19 (38)

The differences of autonomic symptoms between patients with TLE and ELE are shown in Table 2. Twenty-five (50%) patients had ≥2 autonomic symptoms in the patient group, whereas only 5 (11.9%) had ≥2 autonomic symptoms in the control group. Moreover, two or more autonomic symptoms were more common in the TLE group (85.7%) than in the ELE group (24.1%). The rate of OH was significantly higher in patients with TLE (57.1%) than in those with ELE (20.7%).

The SSR amplitudes of the patient group were significantly higher than in the control group (p=0.023); no difference was found in regard to SSR latency between the two groups (Table 3).

The comparison of SSR amplitude and latency values between the epilepsy patient subgroups is shown in Table 4. The TLE and ELE groups showed no differences in terms of SSR amplitude and latency (p>0.05). However, SSR amplitudes were significantly diminished in patients with temporal lobe seizures compared with those with generalized epilepsy (p=0.006). There was no significant difference between these two groups in terms of SSR latency (p>0.05).

The RR-IV% values at rest, during deep inspiration, and during Valsalva maneuvers were significantly lower in the patient group than in the control group (p<0.01 for each) (Table 5). There were no significant differences in RR-IV% values between the patients with temporal or extratemporal lobe seizures or between patients with temporal or generalized seizures (p>0.05 for each) (Table 6).

Table 2. Comparison of autonomic symptoms between patients with temporal and extratemporal lobe seizures

	Type of seizure		
	Temporal (n=21)	Extratemporal (n=29)	
	Number (%) of subjects	Number (%) of subjects	p
Two or more autonomic symptoms	18 (85.7)	7 (24.1)	0.001[m]
Autonomic Symptoms			
Orthostatic intolerance	12 (57.1)	6 (20.7)	0.019[m]
Secretomotor	17 (81)	9 (31)	0.001[m]
Urinary	14 (66.7)	5 (17.2)	0.001[m]
Gastrointestinal	15 (71.4)	3 (10.3)	0.001[m]
Vasomotor	15 (71.4)	14 (66.6)	0.1
Pupillomotor	15 (71.4)	4 (13.8)	0.001[m]

[m]Mann-Whitney U test; p<0.0.5

Table 3. Comparison of SSR values between patient and control groups

SSR	Patients (n=50) mean ± SD (Median)	Controls (n=42) mean ± SD (Median)	p
AMP (μv)	3.51±2.22 (3.22)	2.55±1.92 (1.97)	0.023*
LAT (sn)	1.5±4.88 (1.38)	1.53±0.21 (1.5)	0.1

SSR: sympathetic skin response; AMP: amplitude; LAT: latency; SD: standard deviation
Mann-Whitney U Test
*p<0.05
1patient with no SSR response was excluded

Table 4. Evaluation of SSR values between patients with respect to epilepsy type

	Seizure Type				
	Temporal[a] (n=20) mean ± SD (median)	Extratemporal (n=29) mean ± SD (median)	Generalized (n=12) mean ± SD (median)	p[b]	p[c]
AMP (μV)	2.92±2.01 (2.6)	3.91±2.31 (3.5)	5.53±2.25 (5.14)	0.186	0.006
LAT (ms)	1547.55±525.7 (1415)	1473±468.01 (1370)	1372.5±214.69 (1360)	0.548	0.459

SD: standard deviation; AMP: amplitude; LAT: latency
[a]One subject without an SSR response was excluded from this analysis
[b]Comparison between patients with either temporal or extratemporal seizures, Mann-Whitney U test, p<0.05
[c]Comparison between patients with either temporal or generalized seizures, Mann-Whitney U test, p<0.01

Table 5. Comparison of RR-IV (%) between patient and control groups

	Patients (n=50) mean ± SD (median)	Controls (n=42) mean ± SD (median)	p
At rest (ms)	62.45±101.82 (17.4)	107.79±101.59 (101.4)	0.003**
Deep inspiration (ms)	58.21±77.95 (24.6)	123.49±100.87 (104.5)	0.001**
Valsalva maneuvers (ms)	65.41±84.43 (26.9)	138.18±115.59 (98.8)	0.001**

SD: standard deviation
**Mann-Whitney U test

Table 6. RR-IV (%) between patients with respect to seizure type

	Type of seizure				
	Temporal (n=21) mean ± SD (median)	Extratemporal (n=29) mean ± SD (median)	Generalized (n=12) mean ± SD (median)	p[a]	p[b]
At rest (ms)	104.26±141.67 (16.4)	32.17±39.3 (17.4)	37.49±54.14 (23.7)	0.731	0.940
Deep inspiration (ms)	82.26±109.67 (32.5)	40.8±35.98 (23.8)	45.26±40.12 (29.8)	0.616	0.940
Valsalva maneuvers (ms)	92.27±115.76 (27.8)	45.97±44.4 (26.1)	60.09±59.53 (32.8)	0.701	0.653

SD: standard deviation
[a]Comparison between patients with either temporal or extratemporal seizures, Mann-Whitney U test
[b]Comparison between patients with either temporal or generalized seizures, Mann-Whitney U test

DISCUSSION

Both partial and generalized epilepsies may cause alterations in ANS functions during the ictal period of seizures (1, 7, 8). These functional changes can manifest as cardiovascular, respiratory, gastrointestinal, urinary, cutaneous, or pupillary symptoms (1, 9). Epileptic discharges can also alter ANS functions during the interictal period (1, 10, 11).

Two main mechanisms are assumed to be responsible for the pathophysiologic changes in the ANS of patients with epilepsy; the insula, the central nucleus of the amygdala, the periaqueductal gray matter, and some brainstem nuclei (especially the nucleus solitarius and nucleus ambiguus) may contribute to autonomic dysfunction during seizure activity. Hypersynchronized neuronal discharges may stimulate these nuclei directly or indirectly via the limbic structures. On the other hand, the central autonomic network itself may be a potential contributor to epileptogenesis (12-14).

Interictal autonomic modulations, especially cardiac dysfunctions, are believed to be responsible for SUDEP (15). In a study focused on the mortality of patients with epilepsy, SUDEP was reported in 18% of deaths in these patients (16). Altered cardiovascular autonomic regulation with sympa-

thetic overactivation and parasympathetic reduction have proven to be significant risk factors for SUDEP in patients with epilepsy.

There are several studies on interictal autonomic dysfunction in temporal lobe seizures (11, 17-20). Early and prominent effects on autonomic function can be anticipated in seizures involving this region because temporal lobe structures have numerous connections with the autonomic efferent nuclei. In our study, we observed significantly higher rates of some autonomic symptoms such as vasomotor, urinary, gastrointestinal, secretomotor, and pupillomotor symptoms in patients with TLE compared with ELE. Fifty percent of our patients had at least two clinical autonomic symptoms and most of these patients were in the TLE group (85.7%, p=0.001). Orthostatic hypotension rates were also higher in the TLE group. OH is typically suggestive of sympathetic withdrawal and may support cardiac autonomic dysregulation in our patient cohort. Our findings are compatible with other studies suggesting altered autonomic function in TLEs (11, 17-20).

In the study of Drake et al., who compared 50 patients with epilepsy and healthy controls, the authors reported significantly diminished RR-IV% at rest within the patient group (19.14±12.3 milliseconds) compared with the control group (65.8±52.5 milliseconds) (p<0.01) during the interictal period (14). In concordance with this study, we found significantly lower RR-IV% values at rest, during deep inspiration, and during Valsalva maneuvers in our patient group (p<0.01); however, we found no significant difference in terms of RR-IV% between patients with temporal versus extratemporal seizures or between patients with temporal versus generalized seizures (p>0.05 for both comparisons).

Some researchers have assumed that RR-IV is under parasympathetic system control and will diminish or disappear in the presence of parasympathetic dysfunction (19-20). The reduction in heart rate variability is blamed as one of the pathophysiologic factors of cardiac mortality and sudden cardiac deaths, hence it is expected to contribute to the mechanisms of SUDEP (21). Our results of low HRV may be assumed as a mark of autonomic dysfunction in patients with epilepsy. However, despite the exclusion criteria of the present study, factors such as the nature of epilepsy disease, probable subclinical seizures, the disorganized cognitive status of the patients, problems related to patient compliance with examinations, and development of a possible autonomic neuropathy may have affected our outcomes (16-19).

In the study of Drake et al., SSR latencies and amplitudes were also compared between patient and control groups (14). They found that SSR latency of epilepsy patients were significantly longer (3.34±1.8 seconds vs. 1.29±0.32 seconds) (p<0.05) and SSR amplitudes were significantly higher (1.41±1.20 mV vs. 0.80±0.49 mV) than in the control group (p<0.05). In the study of Berilgen et al., SSR latencies were longer in the upper extremity of the partial epilepsy group when compared with the control group (1.3±0.2 seconds vs. 1.2±0.3 seconds; p<0.05) (22). However, they reported no difference for SSR amplitudes between patients and controls (p>0.05). In our study, we found higher SSR amplitudes in the patient group than in the control group (p<0.05), but there was no significant difference between the two groups in terms of SSR latency (p=0.1). Moreover, we found no significant difference between the TLE and ELE groups in terms of SSR latencies or amplitudes. In addition, although the SSR latency did not differ between patients with either temporal or generalized seizures, the SSR amplitudes were higher in the generalized epilepsy group (p<0.01).

It is thus still controversial whether a high SSR amplitude is indicative of pathologically increased sympathetic responsiveness (23). Sympathetic skin responses are thought to receive suprasegmental excitatory inputs from the cerebral cortex and suprasegmental inhibitory inputs from the striatum and reflect the activity of the posterior hypothalamus and the brain stem reticular formation (23). This may indicate a central steering effect on autonomic functions. We assumed that the significantly higher SSR amplitudes in our patients with generalized epilepsy might be explained by excitatory discharges affecting a more widespread area of the cerebral cortex in generalized seizures.

Akyüz and Akdeniz-Leblebiciler suggested that SSR latency reflected the conduction of the efferent sudomotor pathway and the postganglionic non-myelinated C fibers (24). Other studies reported prolonged SSR latencies in the upper extremities reflecting a sympathetic dysfunction (11, 25-27). Prolonged SSR latencies have also been reported in diseases such as Parkinson's disease, reflex sympathetic dystrophy, amyotrophic lateral sclerosis, and hemispheric and brainstem-derived ischemic strokes where the ANS is extensively involved (28-31). It is hypothesized that sympathetic system dysfunction may be more objectively reflected by SSR latency values because they are less affected by the habituation phenomenon (17). Interestingly, in our study, the SSR latencies between the patient and control groups revealed no significant difference, contrary to the results of the above-mentioned studies.

There are some limitations to our study. First, our small sample size might have affected our outcomes. Second, we could not perform any other additional EPTs such as standard deviation of heart rate variability, expiration/inspiration ratio, Valsalva ratio or frequency analysis, which might support our findings. Moreover, we also could not assess the potential effects of the age and sex of the patients or the frequency of seizures on autonomic functions.

In this study, our objective was to demonstrate the presence of alterations within autonomic system functions in patients with epilepsy during the interictal period. The recognition of patients with autonomic dysfunction is crucial, because it plays an important role in SUDEP. Further studies with larger sample sizes and additional investigations are needed to support our findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine ethics committee (Date 08.06.2009, Decision number: 16988).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.K.S., S.N.Y.; Design – F.K.S.; Supervision – A.Ç.A.; Resources – A.Ç.A.; Materials – S.N.Y.; Data Collection and/or Processing – A.Ç.A.; Analysis and/or Interpretation – A.Ç.A.; Literature Search – A.Ç.A.; Writing Manuscript – A.Ç.A.; Critical Review – F.K.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Wannamaker BB. Autonomic nervous system and epilepsy. Epilepsia 1985; 26(Suppl 1): 31-9. [CrossRef]
2. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med 2011; 365: 1801-1811. [CrossRef]
3. Illigens BM, Gibbons CH. Sweat testing to evaluate autonomic function. Clin Auton Res 2009; 19: 79–87. [CrossRef]
4. Ravits JM. AAEM minimonograph #48: autonomic nervous system testing. Muscle Nerve 1997; 20: 919-937. [CrossRef]
5. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 2012; 87: 1196-1201. [CrossRef]
6. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011; 21: 69-72. [CrossRef]
7. Cechetto DF. Neuropathology and cardiovascular regulation. In: Ter Horst GJ ed. The nervous system and the heart. Humana Press, New Jersey 2000. pp. 159-179. [CrossRef]
8. Schraeder PL, Lathers CM. Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death. Epilepsy Res 1989; 3: 55-62. [CrossRef]
9. Devinsky O. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 2004; 4: 43-46. [CrossRef]
10. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 2000; 41: 42-47. [CrossRef]
11. Isojärvi JI, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllylä VV. Interictal cardiovascular autonomic responses in patients with epilepsy. Epilepsia 1998; 39: 420-426. [CrossRef]
12. Baumgartner C, Olbrich A, Lindinger G, et al. Regional cerebral blood flow during temporal lobe seizures associated with ictal vomiting: an ictal SPECT study in two patients. Epilepsia 1999; 40: 1085-1091. [CrossRef]
13. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc 1993; 68: 988-1001. [CrossRef]
14. Drake ME Jr, Andrews JM, Castleberry CM. Electrophysiologic assessment of autonomic function in epilepsy. Seizure 1998; 7: 91-96. [CrossRef]
15. Frysinger RC, Harper RM. Cardiac and respiratory correlations with unit discharge in epileptic human temporal lobe. Epilepsia 1990; 31: 162-171. [CrossRef]
16. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001; 56: 519-525. [CrossRef]
17. Devinsky O, Perrine K, Theodore WH. Interictal autonomic nervous system function in patients with epilepsy. Epilepsia 1994; 35: 199-204. [CrossRef]
18. Diehl B, Diehl RR, Stodieck SR, Ringelstein EB. Spontaneous oscillations in cerebral blood flow velocities in middle cerebral arteries in control subjects and patients with epilepsy. Stroke 1997; 28: 2457-2459. [CrossRef]
19. Lathers CM, Schraeder PL. Review of autonomic dysfunction, cardiac arrhythmias, and epileptogenic activity. J Clin Pharmacol 1987; 27: 346-356. [CrossRef]
20. Massetani R, Strata G, Galli R, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. Epilepsia 1997; 38: 363-369. [CrossRef]
21. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998; 30: 77-83. [CrossRef]
22. Berilgen MS, Sari T, Bulut S, Mungen B. Effects of epilepsy on autonomic nervous system and respiratory function tests. Epilepsy Behav 2004; 5: 513-516. [CrossRef]
23. Liveson, JA, Ma DM. Laboratory reference for clinical neurophysiology. Davis, Philadelphia 1993; pp. 401–404.
24. Akyüz G, Akdeniz-Leblebiciler M. Anatomy and assessment of the autonomic nervous system. Turk J Phys Med Rehab 2012; 58(Supp 1): 1-5.
25. Fusina S, Conte S, Bertolasi L, Fincati E, Nardelli E, Bongiovanni LG. Sympathetic skin response asymmetry in early stage idiopathic Parkinson's disease. Clin Neurolophysiol 1999; 110: 358-366. [CrossRef]
26. Oz O, Taşlıpınar A, Yücel M, et al. Electrophysiological assessment of the autonomic nervous system in male patients with acromegaly. Eur Neurol 2011; 66: 1-5.
27. Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 1990; 47: 659-664. [CrossRef]
28. Barron SA, Mazliah J, Bental E. Sympathetic cholinergic dysfunction in amyotrophic lateral sclerosis. Acta Neurol Scand 1987; 75: 62-63. [CrossRef]

29. Korpelainen JT, Tolonen U, Sotaniemi KA, Myllylä VV. Suppressed sympathetic skin response in brain infarction. Stroke 1993; 24: 1389-1392. [CrossRef]
30. Oey PL, Vos PE, Wieneke GH, Wokke JH, Blankestijn PJ, Karemaker JM. Subtle involvement of the sympathetic nervous system in amyotrophic lateral sclerosis. Muscle Nerve 2002; 25: 402-408. [CrossRef]
31. Schwalen S, Altermann A, Jorg J, Berg K, Cramer BM. Bilateral suppression of the sympathetic nervous system in hemispheric brain infarction. J Neurol 1996; 243: 157-160. [CrossRef]