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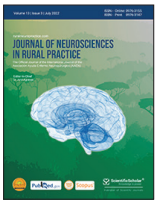

Original Article

Comparative study on autonomic dysfunction in idiopathic generalized epilepsy

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ABSTRACT

Objectives: Autonomic nervous system symptoms are frequently observed in patients with epilepsy. Our objective was to investigate the alterations in autonomic function in idiopathic generalized epilepsy (IGE) patients compared to age- and sex-matched Patients without Epilepsy (PwoE).

Materials and Methods: Thirty patients with epilepsy who had the disease for 6 months–15 years and were controlled or partially controlled with antiepileptic medications, along with a group of healthy PwoEs, underwent Autonomic Function Tests after providing informed consent. The tests measured heart rate variability and blood pressure (BP) responses, and the results were statistically analyzed using Ewing's and Bellavere's criteria to classify cardiac autonomic neuropathy (CAN).

Results: The two groups were demographically comparable. Abnormal breathing patterns, abnormal Valsalva ratios, abnormal hand grip test results, and abnormal BP response were more prevalent in the people with epilepsy (PwE) group than in the PwoE group, and these were statistically significant. There were 18 (60.0%) subjects in the PwE group and none in the PwoE in the definite CAN category (score 4–6). Early CAN was noted in both groups but was slightly more prevalent in the PwE group. Most patients (50.0%) were undergoing treatment for periods ranging from 1 to 2 years, and levetiracetam was the most commonly used anti-seizure medication (ASM). Valproate was associated with the highest proportion of abnormal CAN, followed by levetiracetam and phenytoin.

Conclusion: This study demonstrates that patients with IGE exhibit a significantly higher prevalence of autonomic dysfunction compared to healthy PwoEs, drawing attention to the need for further investigation into the underlying mechanisms and clinical implications.

Keywords: Autonomic function tests, CAN, Epilepsy, People with epilepsy

INTRODUCTION

Autonomic symptoms often occur alongside epileptic seizures, either complementing other seizure manifestations or serving as the primary expression of the seizure itself. Activation of the central autonomic network (CAN) plays a mediating role in these processes.[1] The CAN implicated in the pathophysiology of autonomic epilepsies is predominantly located in the CAN non-dominant hemisphere.[2]

Seizures can be accompanied by a range of autonomic symptoms, including changes in cardiovascular function, alterations in respiratory patterns, disturbances in the gastrointestinal tract, manifestations on the skin, pupillary symptoms, effects on genital and sexual functions, and urinary system involvement.[3,4] These conditions might result from an overactive sympathetic nervous system (NS), although the parasympathetic NS also plays a role, particularly in symptoms related to cardiovascular autonomic dysfunction.[5] Specific autonomic manifestations can offer insights into the location and lateralization of the seizure origin.[6]

A focal seizure may initially manifest primarily through autonomic symptoms; in such cases, these seizures are classified as focal-onset autonomic seizures. Autonomic symptoms of clinical relevance that accompany seizures, whether of focal, generalized, or unknown origin, are classified on the basis of observable characteristics.[1] Symptoms of autonomic dysfunction can manifest in various forms, ranging from mild signs to critical, life-threatening incidents which may include postictal generalized electroencephalogram (EEG) suppression, apnea, and bradycardia, which can ultimately lead to fatal asystole.[6] People with epilepsy (PwE), especially those who have experienced uncontrolled seizures for an extended period, demonstrate noticeable changes in resting autonomic function.[7] The autonomic NS (ANS) may experience functional alterations due to epilepsy, including a reduction in heart rate variability (HRV).[4] Research utilizing

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brief or extended (24-h) electrocardiogram monitoring has shown reduced HRV in individuals with chronic epilepsy, particularly during the period preceding seizures.[8-10] We studied autonomic function in patients with idiopathic generalized epilepsy (IGE) and in healthy Patients without Epilepsy (PwoEs).

MATERIALS AND METHODS

This comparative study was carried out at the Neurology Department of the JSS Hospital, Mysuru, from November 2023 to May 2024. Ethical clearance was obtained from the JSS Institutional Ethical Committee (No. 278; date: October 30, 2023). All participants provided their written informed consent before taking part in the study.

Inclusion criteria

- Patients aged 20–60 years
- Diagnosed with IGE.

Exclusion criteria

- Pregnant and lactating women
- Patients with inflammatory diseases
- Patients with Parkinson's disease and Parkinson's plus diseases
- Patients with thyroid disorders
- Patients with pre-existing heart failure and reduced ejection fraction (<40%)
- Critically ill patients.

Groups

- PwEs – 30 patients diagnosed with IGE according to the international league against epilepsy (ILAE) Classification of 2017 were recruited for this study.
- PwoEs – 30 participants with age- and sex-matched healthy individuals were selected as PwoEs.

All patients underwent evaluation based on the standard protocol at our center. The illness duration ranged from 6 months to 15 years. The healthy PwoEs were selected and subjected to the same battery of tests. Among the 30 PwEs, three patients had controlled seizure frequency ranging from 1 attack/month to 1–3 attacks/week, and the EEG records showed interictal spike/sharp wave discharges and generalized spike-wave or polyspike wave with a normal background. Five patients were taking 2 appropriately chosen antiepileptic drugs (AEDs), including sodium valproate and levetiracetam.

Participants aged 20–60 years with IGE were included whereas pregnant and lactating women, patients with inflammatory diseases, Parkinson's and Parkinson's plus disease, thyroid disorder, pre-existing heart failure with a reduced ejection fraction <40%, and critically ill patients were excluded from the study. All the study participants were directed to refrain from consuming food, alcoholic beverages, caffeinated drinks (including coffee, cola, and tea), energy drinks, tobacco products, and drugs that could affect AS for a minimum of 4 h on the day of the scheduled test. In addition, they were intimated to avoid engaging in activities that might influence blood pressure (BP), such as running or jumping, for 2 h before the testing sessions. The participants were instructed to wear comfortable attire and bathe in the evening before the examination. They were advised against applying any powders, body lotions, or creams below the neckline. In addition, they were encouraged to consume water and maintain adequate hydration.

Before conducting autonomic function tests, each participant's clinical history, demographic information, and data of physical examination results were documented. ANS function tests were performed in a tranquil environment with a controlled ambient room temperature of 22 ± 2°C. Simple resting HRV, delta HRV with deep breath test, Valsalva ratio variability to isometric hand grip, diastolic BP to cold pressor test, and systolic BP variability to head tilt test/lying to standing were recorded as part of the autonomous function test package using the Power-Lab D 40 machine. Ewing's and Bellavere's criteria were used to classify CAN. Ewing's and Bellavere's criteria were used to classify CAN.

The data were statistically analyzed using the Statistical Package for the Social Sciences (version 2). Variables that are categorical were calculated as counts and percentages as well as analyzed using the Chi-square test. A significance level of 5% was considered statistically significant.

RESULTS

The subjects' ages ranged from 19 to 60 years, with a mean age of 38.7 ± 13.13 years, comparable between groups. Age distribution was 30% (19–30 years), 43.3% (31–50 years), and 26.7% (51–60 years). There were 40% females and 60% males in both groups. The subjects' ages ranged from 19 to 60 years, with a mean age of 38.7 ± 13.13 years, comparable between groups. Age distribution was 30% (19–30 years), 43.3% (31–50 years), and 26.7% (51–60 years). There were 40% females and 60% males in both groups.

Participants were divided into three groups based on test scores: Normal (>15 bpm), borderline (10–15 bpm), and abnormal (<10 bpm). In the abnormal category, 46.7% were PwEs, and 6.7% were PwoEs, while in the normal category, 36.7% were PwEs and 63.3% were PwoEs.

The Valsalva ratio was categorized as normal (>1.40), borderline (1.1–1.39), and abnormal (<1.1). About 33.3% of PwEs and 76.7% of PwoEs were in normal range. In the abnormal category, 40% were PwEs, and 16.7% belonged to PwoEs. In the handgrip test, 20% of PwEs and 83.3% of

PwoEs were in the normal category, while 56.7% of PwEs were abnormal, no subjects in the PwoE fell in this category. Borderline categories for both tests included 16.7% to 23.3% of subjects. Overall, PwEs showed higher abnormal results in both tests compared to PwoEs (Chi-square – 28.97, *P*= 0.001*).

BP from standing to lying posture was compared between PwEs and PwoEs. In the normal category, 33.3% of PwEs and 86.7% of PwoEs showed normal responses. In the borderline category, 36.6% of PwEs and 13.3% of PwoEs were borderline. In the abnormal category, 30% of PwEs showed abnormal responses, with none of the subjects in the PwoE group showing abnormal responses. The Chi-square test indicated a statistically significant association between PwEs as well as PwoEs, suggesting abnormal breathing patterns, abnormal Valsalva ratios, abnormal hand grip strength, and abnormal BP response [Table 1].

The types of autonomic dysfunction were categorized as normal, parasympathetic, sympathetic, and both (sympathetic and parasympathetic dysfunction)**.** Both parasympathetic and sympathetic dysfunction were found in 16 (53.3%) subjects in the PwE (Patients with Epilepsy) and 3 (10.0%) in the PwoE. The normal category included 4 (13.5%) subjects in the PwE and 23 (76.7%) in the PwoE, accounting for 45.0% of the overall sample. In the parasympathetic category, there were 3 (10.0%) subjects in the PwE and 4 (13.3%) in the PwoE. The sympathetic category included 7 (23.3%) subjects in the PwE and none in the PwoE.

Table 1: Distribution of the subjects based on deep breathing test, Valsalva maneuver, and BP response to standing from lying posture to assess the decrease in systolic BP (mmhg).

	Groups		Total (%)
	PwEs (%)	PwoEs (%)	
Deep breathing test (bpm)			
Normal >15	11 (36.7)	19 (63.3)	30 (50.0)
Borderline 10–15	5 (16.7)	9 (30.0)	14 (23.3)
Abnormal <10	14 (46.7)	2 (6.7)	16 (26.7)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 12.27, *P*=0.002*			
Valsalva ratio			
Normal >1.40	10 (33.3)	23 (76.7)	33 (55.0)
Borderline 1.1–1.39	8 (26.7)	2 (6.7)	10 (16.7)
Abnormal <1.1	12 (40.0)	5 (16.7)	17 (28.3)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 11.60, *P*=0.003*			
BP response to standing from lying posture			
Normal <15	10 (33.3)	26 (86.7)	36 (60.0)
Borderline 15–20	11 (36.6)	4 (13.3)	15 (25.0)
Abnormal >20	9 (30.0)	0 (0.0)	9 (15.0)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 19.37, *P*=0.001*			

*Significant. BP: Blood pressure, PwEs: Patients with epilepsy, PwoEs: Patients without epilepsy

In the definite CAN category, there were 6 (20.0%) subjects from the PwE and none from the PwoE. The early CAN category included 4 (13.3%) subjects from the PwE and 7 (23.3%) from the PwoE, accounting for 18.3% of the overall sample. The normal category comprised 3 (10.0%) subjects from the PwE and 23 (76.7%) from the PwoE, accounting for 43.3% of the total sample. In the severe CAN category, there were 17 (56.7%) subjects in the PwE and none in the PwoE, representing 28.3% of the overall study sample. There were 18 (60.0%) subjects in the PwE and none in the PwoE in the definite CAN category (score 4–6), representing 30.0% of the overall sample. The early CAN category (score 2–3) included 9 (30.0%) subjects from the PwE and 7 (23.3%) from the PwoE, accounting for 26.7% of the total sample. The No CAN category (score 0) comprised 3 (10.0%) subjects from the PwE and 23 (76.7%) from the PwoE, accounting for 43.3% of the overall study sample. The Chi-square test showed a significant association between autonomic dysfunction, Ewing's category, and Bellavere's criteria. Sympathetic and parasympathetic dysfunctions were more prevalent in PwEs, while normal autonomic function was more common in PwoEs. Severe and definite CAN was more frequent in PwEs, with early CAN more prevalent in PwEs [Table 2].

Regarding treatment duration, 20.0% of the subjects received treatment for 6 months or less, while the majority (50.0%) received treatment for a period ranging from 1 to 2 years. A smaller proportion (16.7%) of patients were treated for 3–4 years, and 13.3% received treatment for 5 years or longer. Levetiracetam was the most commonly prescribed medication for 12 (40.0%) subjects. Phenytoin and sodium valproate were prescribed for 8 (26.7%) and 10 (33.33%) subjects, respectively [Table 2].

Among the 30 subjects, 12 were on levetiracetam, 8 on phenytoin, and 10 on valproate. Of the patients on levetiracetam, 75% had abnormal CAN, whereas 25% had normal CAN. For those on phenytoin, 62.5% exhibited abnormal CAN, while 37.5% had normal CAN. The highest percentage of abnormal CAN was observed in the Valproate group, with 90% of patients showing abnormal CAN, and only 10% had normal CAN. The overall prevalence of abnormal CAN across all drug groups was 76.7%, while 23.3% of patients had normal CAN. The Chi-square test showed no statistically significant association between the drug type and the presence of abnormal CAN [Table 3].

DISCUSSION

This study investigated whether differences in autonomic cardiovascular PwoE could occur between IGE and

healthy PwoEs. Our findings demonstrate that autonomic function was more prevalent in PwEs than in PwoEs. This may be attributed to ANS dysfunction in patients with epilepsy, especially in the parasympathetic NS, which normally conveys respiration signals to the heart and other physiological signals. Multiple factors may contribute to the higher variability and reactivity of autonomic function observed in PwE, including (a) effects of medication, (b) structural lesions in patients, (c) hospitalization-related conditioning, and (d) chronic epilepsy effects.

Table 2: Autonomic dysfunction classification in epilepsy patients and drugs used.

	Groups		Total (%)
	PwEs (%)	PwoEs (%)	
Type of autonomic dysfunction			
Both	16 (53.3)	3 (10.0)	19 (31.7)
Normal	4 (13.3)	23 (76.7)	27 (45.0)
Parasympathetic	3 (10.0)	4 (13.3)	7 (11.7)
Sympathetic	7 (23.3)	0 (0.0)	7 (11.7)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 29.40, *P*=0.001*			
Ewing's category			
Definite CAN	6 (20.0)	0 (0.0)	6 (10.0)
Early CAN	4 (13.3)	7 (23.3)	11 (18.3)
Normal	3 (10.0)	23 (76.7)	26 (43.3)
Severe CAN	17 (56.7)	0 (0.0)	17 (28.3)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 39.20, *P*=0.001*			
Category Bellavere			
Definite CAN (Score-4–6)	18 (60.0)	0 (0.0)	18 (30.0)
Early CAN (Score-2–3)	9 (30.0)	7 (23.3)	16 (26.7)
No CAN (Score-0)	3 (10.0)	23 (76.7)	26 (43.3)
Total	30 (100.0)	30 (100.0)	60 (100.0)
Chi-square - 33.63, *P*=0.001*			
Drug (%)			
Levetiracetam	12 (40)		
Phenytoin	8 (26.67)		
Sodium Valproate	10 (33.33)		
Total	30 (100.0)		

*Significant . CAN: Cardiac autonomic neuropathy, PwEs: Patients with epilepsy, PwoEs: Patients without epilepsy

Overall, the majority of study participants (75%) exhibited signs of autonomic dysfunction. Such autonomic manifestations have been commonly noted by other investigators also.[6,11-13] These phenomena are frequently observed during or following IGE seizures.[12-14] It was proposed that repeated epileptogenic events affecting or spreading to these regions may lead to progressive alterations in CANs.[15,16]

IGE patients PwEs exhibited a notably higher prevalence of ANS symptoms than those in the PwoE. This highlights the role of the temporal lobe in regulating CAN, with epilepsy disrupting autonomic function, which in turn causes neuronal degeneration in the amygdala and hippocampus.[17,18]

Delta heart rate (HR), Valsalva ratio, BP changes, and handgrip test results indicate parasympathetic and sympathetic dysregulation, suggesting an interrelationship between the brain and heart in PwE.[4,19-21] Cardiac symptoms associated with epilepsy can manifest not only during seizures but also between episodes.[10,22] Evidence for this has been observed in various forms of epilepsy, including IGE.[23,24] A recent theory suggests that the "epileptic heart" develops due to recurring increases in catecholamines and hypoxemia during chronic epilepsy and these factors are thought to damage the heart and coronary blood vessels, leading to impairments in both electrical and mechanical cardiac function.[25,26]

CAN was diagnosed using Ewing's and Bellavere category tests, and CAN was found to be more common in epileptic PwEs than in the PwoE group. The autonomic function is frequently affected by generalized seizures, not only during the seizure itself but also during the periods between seizures and subsequent occurrences. Seizure-related autonomic dysfunction may lead to changes in heart and lung functions, potentially contributing to unexpected fatalities in IGE. When seizures originate from or propagate to regions within the CAN, they can simulate the activation of autonomic afferents or alter autonomic expression. The CAN comprises

Table 3: Association of Ewing's criteria with drugs taken.

Ewings category	Drug			Total (%)
	Levetiracetam (%)	Phenytoin (%)	Valproate (%)	
Abnormal CAN	9 (75.0)	5 (62.5)	9 (90.0)	23 (76.7)
Normal CAN	3 (25.0)	3 (37.5)	1 (10.0)	7 (23.3)
Total	12 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)

Chi-square value-1.91, *P*=0.38, CAN: Cardiac autonomic neuropathy.

cortical limbic regions, including the amygdala, anterior insula, anterior cingulate cortex, and posterior orbitofrontal cortex.[27] These regions are directly connected to subcortical areas within the CAN, encompassing the hypothalamus, periaqueductal gray region, parabrachial region situated in the pons, nucleus of the solitary tract, and ventrolateral medulla. The autonomic function can be modified, and visceral and emotional sensations can be triggered by both electrical stimulation and spontaneous seizures that originate in or spread to the cortical limbic regions.

The majority of the participants in PwEs were under treatment for 1–2 years. Levetiracetam was the most used AED in IGE patients, followed by sodium valproate and phenytoin. The link between AEDs and cardiac autonomic neuropathy development remains a subject of debate, while some researchers have not found any link between AED therapy and autonomic dysfunction during interictal periods.[8,28-30] Majority of IGE patients were on levetiracetam in our study.

The present study investigated the autonomic dysfunction in epilepsy, focusing on clinical tests while Sivakumar *et al*., study focused on biomarkers. In Sivakumar *et al*., study, HRV analysis found enhanced parasympathetic activity in epilepsy, with stronger respiratory sinus arrhythmia (RSA) power (97% higher in epilepsy) and lower HR (21% lower in epilepsy). RSA power and HR could serve as biomarkers for epilepsy, with RSA having 57% sensitivity and 100% specificity, and HR showing 73% sensitivity and 76% specificity and there were no significant differences in resting BP in epilepsy patients,[31] whereas the present study focused on broader autonomic dysfunction, noting the higher prevalence of abnormal Valsalva ratios (40% in epilepsy vs. 16.7% in PwoEs) and severe cardiac autonomic neuropathy (56.7% in epilepsy vs. 0% in PwoEs) and observed a higher prevalence of abnormal BP responses in epilepsy patients, indicating a more prominent autonomic dysfunction in this group, particularly in relation to postural changes.

The findings of the present study found that Valproate was associated with the highest proportion of abnormal CAN, followed by levetiracetam and phenytoin. However, no statistically significant association was found between the type of ASM and the presence of abnormal CAN. This lack of significance suggests that factors other than the specific ASM may play a role in the development of autonomic dysfunction in patients with IGE. Valproate, while being effective in controlling seizures in IGE, was found to be associated with a relatively high prevalence of autonomic dysfunction in the present study. This supports previous research that has noted a higher incidence of autonomic symptoms in patients treated with.[32] The choice of ASM may not solely dictate autonomic outcomes, showing the role of individual patient factors and comorbidities.[33,34] The medication's potential to cause autonomic dysfunction may be linked to its pharmacological effects on the central NS, though this relationship is still not fully understood. The choice of ASM in epilepsy treatment is influenced by a complex interplay of factors, including drug efficacy, safety, and side-effect profiles, with autonomic dysfunction being one such side effect. However, the study's results suggest that the type of ASM alone may not be the primary determinant of autonomic dysfunction. Rather, it could be influenced by the underlying pathophysiology of epilepsy itself.[32] The results contribute to the growing body of evidence suggesting that further research is necessary to fully understand the complex interactions that lead to autonomic dysregulation in epilepsy.

A limitation of this study is the small sample size, as only 30 patients with epilepsy and a group of healthy PwoEs were included and a larger study has to be done with a larger sample and different drug types to know the exact correlation. This limited sample may affect the generalizability of the findings.

CONCLUSION

A significant prevalence of autonomic dysfunction was observed in patients with IGE compared to healthy PwoEs. Abnormal results observed in deep breathing, Valsalva ratio, handgrip strength, and BP response were observed in the IGE group. Both sympathetic and parasympathetic dysfunctions were more common and severe CAN was more prevalent in IGE patients. These findings suggest that IGE may lead to widespread autonomic dysfunction, showing the need for further investigation into the underlying mechanisms and potential clinical implications for patient care.

Ethical approval: The research/study was approved by the Institutional Review Board at JSS Institutional Ethical Committee, number 273, dated October 30, 2023.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
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