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Levetiracetam efficacy on frontal lobe dysfunctions and anger rumination in patients with epilepsy

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ABSTRACT

This study compared the frontal lobe functioning and anger rumination between patients with epilepsy and healthy individuals. The second objective was to examine the efficacy of levetiracetam therapy on frontal lobe dysfunctions and anger rumination in patients with epilepsy. Participants (50 patients with epilepsy and 50 healthy individuals) completed the Frontal Assessment Battery (FAB) and Anger Rumination Scale (ARS). The patients had two testing sessions: pre- and post-levetiracetam therapies. The results showed that patients with epilepsy had frontal lobe dysfunctions in contrast with healthy individuals. Patients with epilepsy had higher anger rumination than healthy individuals. Compared with baseline performance, frontal lobe dysfunctions and anger rumination were significantly reduced after three months of levetiracetam therapy in patients with epilepsy. It is concluded that levetiracetam therapy may be beneficial in improving frontal lobe functioning and anger rumination thought pattern in patients with epilepsy. However, further studies are required to confirm this evidence.

1. Introduction

Levetiracetam (S-enantiomer of alpha-ethyl-2-oxo-1-pyrollidine acetamide) is an antiepileptic second-generation drug used as an add-on or monotherapy treatment for partial, generalized tonic–clonic seizures [1,2]. It has a unique structure and mechanism of action unlike other antiepileptic drugs (AEDs). Levetiracetam binds to 2A (synaptic vesicle protein), inhibits calcium release from intraneuronal stores, opposes activity of gamma-aminobutyric acid (GABA) and glycin-gated currents (negative modulators), and inhibits interneurons' extreme synchronized activity and calcium channels (N-type). It is rapidly absorbed with high oral bioavailability and has minimal metabolism consisting of hydrolysis of acetamide group and renal elimination. Other unique features of the drug includes the lack of cytochrome P450 (isoenzyme-inducing potential) and no significant pharmacokinetic interactions with AEDs or any other drugs [3]. It is a broad-spectrum drug and an effective treatment to reduce epileptic seizures. Levetiracetam quickly attains steady state concentrations and linear kinetics. It has minimal plasma protein binding [4].

During recent years, levetiracetam captured the attention of researchers because of its role as a cognitive enhancer. Few studies have suggested possible positive cognitive effects. For instance, data on electroencephalographic, neuropsychological, and behavioral measures demonstrated that levetiracetam has positive impact on memory, attention, planning, and decision-making through increased theta power in the frontopolar cortex and the anterior frontal cortex and decreased theta power in the prefrontal inferior gyrus in healthy individuals. Acute effect of levetiracetam suggests that specific inhibitory control is achieved which reduces reaction times on choice for perceptual set and generates efficiency in decision-making [5]. Patients with epilepsy showed seizure control and improved cognitive performance after 3 to 6 months of levetiracetam intake [6]. Long-term use of levetiracetam in drug-naïve patients with epilepsy significantly improved cognitive functioning across various areas such as attention, executive function, and mental flexibility [7]. Patients with epilepsy achieved not only seizure freedom but also improved quality of life after long-term use of levetiracetam [8,9]. However, several studies highlighted psychiatric adverse events such as feelings of aggression, hostility, and aggression in patients during levetiracetam therapy [10,11]. After 14 weeks of levetiracetam medication in patients with partial epilepsy, scores on hostility, anger, and mood stability were significantly worse than baseline scores [12]. In patients with a long history of epilepsy who experience aggression, behavioral tolerability of levetiracetam is questionable [13]. Though studies have examined the role of levetiracetam therapy in the experience of anger, aggression, and cognitive functions, little is known about whether levetiracetam would be efficacious in reducing frontal lobe dysfunctions and anger rumination in patients with epilepsy.

This study investigated the effectiveness of levetiracetam on anger rumination and frontal lobe functions. The goal was to clarify the role of levetiracetam therapy in reducing frontal lobe dysfunctions and anger rumination. Rumination of anger is a thinking style concerned

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with repetitive focus on anger-inducing experiences. It is a risk factor for trait anger over time [14]. Studies examining neural correlates of anger rumination suggest that activity in the medial prefrontal cortex is associated with anger rumination and is involved in individual differences related with experience of displaced aggression. However, subsequent self-reported anger rumination following provocation is associated with increased activity in the hippocampus, cingulate cortex, and insula [15]. Given that neural correlates involved in higher order cognition and anger rumination overlap, it was hypothesized that levetiracetam would be effective in reducing cognitive dysfunctions and anger rumination.

2. Methods

2.1. Study design

The study was approved by the board of studies of The Islamia University of Bahawalpur, Pakistan. Study protocol adhered to the ethical standards as prescribed in the Helsinki Declaration. Participants gave written informed consent to participate in this study. The psychologist who collected data and the participants were blinded to the study objectives.

Fifty patients diagnosed with epilepsy at Bahawal Victoria Hospital, Bahawalpur and Nishtar Hospital, Multan, Pakistan participated in the study. The inclusion criteria for patients were as follows: (i) must be 22–45 years; (ii) prescribed levetiracetam therapy by a physician; (iii) must have focal aware, focal impaired awareness, focal to bilateral tonic–clonic, and generalized tonic–clonic seizure type; and (iv) must have at least two generalized onset seizures in the previous three months or at least four focal onset seizures in the previous year, with at least one during the previous three months. Patients were excluded from the study if they (i) had previous exposure to levetiracetam, (ii) were taking AEDs other than levetiracetam, (iii) had history or present symptoms of allergy to any levetiracetam component, and (iv) have any progressive neurological disease. Fifty healthy individuals were included in the study following these criteria: (i) age of 22–45 years, (ii) no present symptoms/history of any neurological or psychological disorder and/or medical condition, and (iii) not taking any medication (see Table 1). None of the enrolled patients reported any side effects of levetiracetam. No subjects who dropped out prior to the 3-month assessment were enrolled.

Table 1
Demographic characteristics of sample ($N = 100$).

	Patients	Healthy individuals	
	$n = 50$	$n = 50$	
	M ± SD	M ± SD	
Age (22–45 years)	34.50 ± 6.65	32.56 ± 6.11	$t(49) = 1.59$, $p = .11$
Gender, n (%)			
Male	50 (25.0)	50 (25.0)	
Female	50 (25.0)	50 (25.0)	
Age at epilepsy onset (years)	30.34 ± 6.46		
Epilepsy duration (years)	4.16 ± 1.28		
Levetiracetam dose per day (mg)	500–2500		
Pathology n (%)			
Idiopathic	20 (40.0)		
Symptomatic	15 (30.0)		
Cryptogenic	15 (30.0)		
Type of seizure, n (%)			
Focal aware	10 (20.0)		
Focal impaired awareness	23 (46.0)		
Focal to bilateral tonic–clonic	11 (22.0)		
Generalized tonic–clonic	06 (12.0)		
Seizure reduction ≥50%	35		
Seizure reduction ≥30%	15		

2.2. Instruments

2.2.1. Frontal Assessment Battery (FAB)

The FAB [16] is a brief neuropsychological battery that assesses cognitive and behavioral functions of the frontal lobe. It is composed of the following six subtests: similarities, motor series, Go–No Go, lexical verbal fluency, conflicting instructions, and prehension behavior. These subtests assess several cognitive functions such as conceptualization, mental flexibility, programming, sensitivity to interference, inhibitory control, and environmental autonomy. Subtests correlate with frontal metabolism measured through regional distribution of fludeoxyglucose F18 in positron emission tomography of patients with frontal lobe damage due to various causes. Total score (range: 0–18, a low score shows impairment) is a composite score on the six neuropsychological subtests (score range is 0–3 each). The FAB is a valid ($r = .82$ with Mattis Dementia Scale) and reliable measure (inter-rater reliability: $k = .87$).

2.2.2. Anger Rumination Scale (ARS)

The ARS [17] is a 19-item self-report measure used to assess anger rumination in clinical practice. Items are rated on a 4-point Likert scale (almost never = 1 to almost always = 4; total score range = 19–76). A higher score corresponds to greater anger rumination. It has good psychometric properties (internal consistency: $\alpha = .93$).

2.3. Procedure

Healthy individuals were tested once. Patients were assessed twice during the study. The first testing session was conducted at the time of diagnosis when patients were not taking any medication in order to determine baseline. The second testing session was conducted after three months of levetiracetam medication to assess the efficacy of levetiracetam on frontal lobe dysfunctions and anger rumination. Participants completed FAB and ARS in a single testing session. Upon completion of instruments, they were debriefed about study objectives and were thanked for their participation.

3. Results

3.1. Statistical analyses

Demographic characteristics were computed through descriptive statistics (Table 1). One-way analysis of variance (ANOVA) was conducted to compare baseline scores of patients and healthy individuals on subscale scores of FAB and ARS, with dependent factors (similarities vs. lexical verbal fluency vs. motor series vs. conflicting instructions vs. Go–No Go vs. prehension behavior vs. ARS total) and group (patients vs. healthy individuals) as fixed factor. A separate repeated measures ANOVA was conducted on each subscale of FAB and total scores on FAB and ARS to assess efficacy of Levetiracetam therapy in patients 2 (pre vs. post treatment; within subject).

Results showed that patients scored significantly lower than healthy individuals on all subscales of FAB: similarities ($F(1, 98) = 516.03$, $p < .001$), lexical verbal fluency ($F(1, 98) = 800.26$, $p < .001$), motor series ($F(1, 98) = 1304.00$, $p < .001$), conflicting instructions ($F(1, 98) = 1320.25$, $p < .001$), Go–No Go ($F(1, 98) = 1897.96$, $p < .001$), prehension behavior ($F(1, 98) = 992.10$, $p < .001$), and total FAB ($F(1, 98) = 5736.78$, $p < .001$) while there was reduction in ARS ($F(1, 98) = 1572.34$, $p < .001$) (Table 2). Posttreatment scores were significantly higher than pretreatment scores on similarities ($F(1, 49) = 180.84$, $p < .001$, $\eta p2 = .78$), lexical verbal fluency ($F(1, 49) = 182.25$, $p < .001$, $\eta p2 = .78$), motor series ($F(1, 49) = 196.00$, $p < .001$, $\eta p2 = .80$), conflicting instructions ($F(1, 49) = 563.50$, $p < .001$, $\eta p2 = .92$), Go–No Go ($F(1, 49) = 564.00$, $p < .001$, $\eta p2 = .92$), prehension behavior ($F(1, 49) = 173.72$, $p < .001$, $\eta p2 = .78$), and total FAB ($F(1, 49) = 1366.21$, $p < .001$, $\eta p2 = .96$) whereas posttreatment scores on ARS were significantly reduced ($F(1, 49) = 564.33$, $p < .001$, $\eta p2 = .92$) (Table 3).