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Research Article

Social cognition and prefrontal cognitive function in patients with epilepsy treated with eslicarbazepine acetate

Abstract

Purpose: The purpose of this study was to evaluate the impact of treatment with eslicarbazepine acetate (ESL) on social cognition and prefrontal cognitive function in adults with partial onset seizures.

Methods: A prospective, single-center, interventional study was conducted in patients aged 18 to 65 years with focal seizures, who received ESL. All patients were assessed using Theory of Mind (ToM) tasks (Eyes test and Faux Pas Recognition test), and evaluation of attentional and executive functions (Wisconsin Card Sorting test [WCST], Symbol Digit, Forward and Backward Digit Span, and Stroop tests), auditory-verbal memory (recognition and total learning memory test), quality of life (QOLIE-31 questionnaire), and anxiety/depression (Hospital Anxiety and Depression Scale [HADS]). Patients were evaluated before and at 6 months after starting ESL.

Results: In total, 41 patients with partial onset epilepsy were prescribed ESL, and 30 completed the follow-up assessment. Results of the Eyes test (p=0.017) and Faux Pas Recognition test (p=0.002) showed a significant improvement in ToM tasks. On stratified analysis by gender, males experienced a greater improvement than females on both tests (p<0.001 and p=0.003, respectively). Cognitive improvement was seen in the WCST results (number of errors p=0.007, and number of perseverations p=0.010), Symbol Digit (p=0.004), Backward Digit Span (p=0.002), and Stroop test (p=0.031). No differences were found in the QOLIE-31 (p=0.145) or HADS (anxiety p=0.516, depression p=0.305) results. Improvements were independent of reductions in the number of seizures and ESL dosing.

Conclusion: ESL treatment may improve some aspects of ToM in patients with epilepsy, specifically in males and regardless of seizure control, with no changes in quality of life, anxiety, or depression status.

Abbreviations

ESL Esclicarbazepine; ToM Theory of Mind; WCST Wisconsin Card Sorting Test; QOLIE   Quality of Life in Epilepsy; HADS Hospital Anxiety and Depression Scale; COWAT Control Oral Word Association; AVLT Auditory Verbal Learning Test; AED AntiEpileptic Drugs

Introduction

Epilepsy is a chronic disorder characterized by an enduring predisposition to experience recurrent seizures, which are often associated with neurobehavioral comorbidities, including cognitive impairment, psychiatric disorders, and social problems that may have an impact on the patient's quality of life [1–4].

Social cognition is a broad concept that refers to the ability to understand the internal mental states of other people and oneself [5]. It involves a variety of cognitive, emotional, and motivational processes that modulate the behavioral responses that enable us to engage in the activities we value. The most representative mechanism of social cognition is Theory of Mind (ToM) [2], a high-order social cognitive skill defined as the ability to understand not only our own thoughts, intentions, beliefs and emotions, but also those of others. ToM, which is essential for social interaction, develops mainly during childhood and adolescence [3] and includes cognitive perspective-taking (cognitive ToM) and emotional understanding (affective ToM).

ToM has been found to be impaired in epilepsy patients [6,7], possibly due to disruption of a widely distributed neural

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network that supports this complex function [5]. In patients with focal epilepsy, earlier onset of the condition may be related to greater ToM impairment, and the location of the epileptic source may have an impact on the severity of ToM dysfunction. Temporal and frontal lobe epilepsies are the main types in which ToM is affected [5]. Although there is little evidence regarding idiopathic generalized epilepsy and ToM, it is known that this condition may interfere with social cognitive processes, such as emotion recognition in faux pas tasks [8,9]. The results of recent research suggest that performance in ToM tasks may be related to changes in other cognitive abilities and executive functions, such as working memory, inhibition of automatic responses, and attentional capacity [5]. In addition, previous studies have reported that long-term use of antiepileptic drugs (AEDs) may have a negative impact on social cognition in patients with epilepsy [10].

Eslicarbazepine acetate (ESL) is a short-acting sodium channel blocker that provides some enhancement of the slow inactivation of voltage-gated sodium channels [11]. ESL is considered a third-generation member of the dibenzazepine family of AEDs, which also includes carbamazepine and oxcarbazepine [12]. In addition to seizure control, this pharmacological group has proven useful in the treatment of mood and behavior disorders [13-15]. No exploratory studies have been performed to assess the effect of these drugs on social cognition.

The primary objective of this study was to evaluate the impact of ESL treatment on social cognition and prefrontal functions in adults with partial onset seizures. The secondary objectives were to assess changes in cognitive function and to record the efficacy and safety of ESL.

Materials and Methods

Study design

This is a prospective, exploratory, single-center study performed in patients initiating ESL in routine clinical practice for the treatment of focal seizures. The study, conducted between January 2015 and June 2016, was approved by the local ethics committee and all patients provided informed consent for participation.

Setting and participants

The patients enrolled ranged in age from 18 to 65 years, had a pre-morbid IQ higher than 80, and a confirmed diagnosis of epilepsy with focal-onset seizures (with or without generalization) according to the criteria of the International League Against Epilepsy (ILAE, 2001). Patients with a neurodegenerative disease, systemic disease with cognitive impairment, symptomatic epilepsy due to progressive disease, a psychiatric disorder (psychosis or major mood disorders in course), or a neurodevelopmental disorder were excluded. Patients meeting the above criteria and considered candidates to start ESL were prospectively included. The decision to prescribe ESL and the dose administered were at the discretion of the attending neurologist in each individual case.

A complete neuropsychological assessment was performed at the baseline visit, before starting ESL. Patients were followed-up for the next 6 months, at which time a second neuropsychological assessment was carried out. The treating neurologists were blinded to the neuropsychological assessments, and the decision to start ESL was based on efficacy, tolerability, and safety parameters.

All patients were prospectively evaluated for several cognitive domains, including ToM tasks, attentional and executive functions, auditory-verbal memory, quality of life, and anxiety and depression.

Interventions and assessments

Baseline characteristics (socio-demographic features, medical history, type of seizures and number of seizures per month) were recorded in a database. All patients underwent two neuropsychological evaluations, one at the baseline visit and one 6 months after starting ESL treatment.

The neuropsychological tests for ToM assessment included the Reading the Mind in the Eyes test [16] and the Faux Pas Recognition test [17]. To evaluate attentional and executive functions, the following tasks were performed: the Wisconsin Card Sorting test to evaluate cognitive flexibility [18], the Stroop test to assess inhibition of automatic response [19], the Trail-making test (Parts A and B) to assess visual attention and task switching [20], the Forward and Backward Digit Span to evaluate attention and working memory [21]. Symbol Digit to assess processing speed [21], the verbal fluency FAS test [22], to evaluate phonetic verbal fluency, and the Control Oral Word Association Test (COWAT) [23] to assess semantic and verbal fluency. Auditory-verbal memory was evaluated by the Auditory Verbal Learning Test (AVLT) through recognition and global learning tasks [24]. In addition, the QOLIE-31 questionnaire [25], was filled out to assess quality of life and the Hospital and Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression [26]. The neuropsychological assessments were performed by two neuropsychologists (A.S. and G.O.), who were blinded to the clinical and treatment data during the follow-up period.

Scales were converted to T scores (normalized scores with a mean value of 50 and a standard deviation (SD) of ±10) and corrected by age and gender. Lower scores indicate poorer performance.

Statistical methods

Descriptive and frequency statistics were obtained and comparisons were carried out using the SPSS statistical package, version 17.0 for Windows. The Wilcoxon signed rank test was performed to assess changes in seizure frequency. A paired-samples t test was used to analyze changes in the neuropsychological test scores, and the McNemar test to assess changes in the categorical variables. General linear models for repeated measures were used to evaluate changes between the different characteristics of the patients and type of epilepsy. A p value <0.05 was considered statistically significant.

Results

Participants

In total, 41 consecutive patients were recruited during the study period, and 30 of the 41 completed the second neuropsychological assessment. Eleven patients dropped out of the study due to adverse events (n=7), dementia (n=1), psychiatric disorder (n=1), or withdrawal of informed consent (n=2). The baseline demographic and clinical data are shown in table 1. Temporal lobe epilepsy was the epilepsy type most often observed (50%, n=15), followed by frontal lobe epilepsy (20%, n=6). The mean duration of epilepsy was 10 years (SD ±11). The reasons for starting ESL were adverse events related to previous AED treatments in 56.7% of patients, no response to previous treatment in 30%, and first-line treatment in 13.3%.

At the baseline visit, 4 patients were treatment-naïve, 21 were receiving AED monotherapy, and 5 were receiving AED polytherapy. Levetiracetam was the drug most commonly used (64.7%, n=11) at the baseline evaluation. ESL titration was tailored to each individual case. The starting ESL dose was 400 mg per day, which was increased by 400 mg after each successive month, if necessary. At the 6-month follow-up, the median ESL dose was 800 mg per day [400-1200].

Seizure frequency and adverse events

The mean number of seizures per month was 1.6±3 SD (0-15) at baseline and 0.4±1 SD (0-5) at the follow-up visit, yielding a 72% reduction. Mild drug-related adverse events occurred in 30% of the patients (n=9), and included drowsiness (n=3), dizziness (n=3), headache (n=2), and anxiety (n=1).

Theory of mind tasks

A significant improvement was observed in the Eyes test (p=0.017) and Faux Pas Recognition test (p=0.002) results (Figure 1, Table 2). Generalized linear models showed that ToM performance was only affected by gender. Males showed a greater improvement than females on the Eyes test (p<0.001) (Figure 2).

Attentional and executive functions

Scores on some of the cognitive tests evaluating attentional and executive functions showed significant improvements: number of errors on the Wisconsin Card sorting test (*p*=0.007) and number of perseverations (*p*=0.010), information processing speed (*p*=0.004), Backward Digit Span (*p*=0.022), and Stroop test (*p*=0.031) (Table 2).

Auditory-verbal memory

We observed significant differences in learning and processing new information (*p*=0.036) and in recognizing learned information (*p*=0.005) (Table 2).

Quality of life, and anxiety and depression

There were no differences in the patients' overall quality

Table 1: Demographic and baseline characteristics of patients at baseline. Values are reported as the number (%), unless otherwise indicated. Values are reported as number (percent).

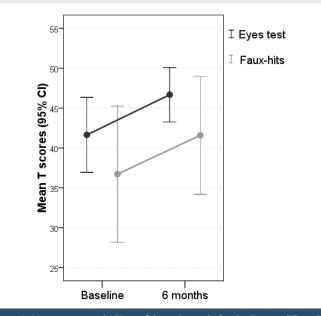|	N=30
Age, years, mean±SD	48.4±14.3
Gender, male	15 (50%)
Duration of epilepsy, years, mean±SD	10.3±11.0
Psychiatric history	5 (16.7%)
Type of seizures	
Simple partial	7 (23.3%)
Complex partial	9 (30%)
Secondary generalized	14 (46.7%)
Type of epilepsy	
Temporal	15 (50%)
Frontal	6 (20%)
Extra-temporal	6 (20%)
Undetermined	3 (10%)
Etiology	
Cryptogenic	12 (40%)
Stroke-related	7 (23.3%)
Traumatic brain injury	3 (10%)
Tumor	2 (6.7%)
Hippocampal sclerosis	2 (6.7%)
Post-encephalitis	2 (6.7%)
Cortical dysplasia	1 (3.3%)
Multiple sclerosis	1 (3.3%)

Figure 1: Mean scores and 95% confidence intervals for the Eyes and Faux Pas tasks at baseline and at 6 months of ESL treatment show significant increases: Eyes test, 41.6 to 46.7 (p=0.017) and Faux Pas test, 36.7 to 41.6 (p=0.002).

of life as evaluated with the QOLIE-31 questionnaire (baseline, 49.4±9.2, 6 months 51.2±9.8; p=0.145) or in the separate subscale results. There were no changes in anxiety (baseline 7.5±3.4, 6 months 7.2±3.4; *p*=0.516) or depression (baseline, 5.4±3.4, 6 months 4.8±3.4; *p*=0.305).

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Table 2: ToM, attentional and executive functions, and auditory-verbal memory results (T scores corrected by age and gender).

		Baseline	At 6 months of treatment	P
ToM Task	Eyes Test	41.6±12.6	46.7±9.2	0.017
	Faux Pas Recognition	36.7±22.8	41.6±19.8	0.002
	Faux Pas control questions	44.7±24.8	51.6±12.5	0.069
Attentional and executive functions	Trail-Making test A	38.9±8.9	41.8±9.2	0.058
	Trail-Making test B	41.6±12.6	44.4±13.6	0.235
	SDMT	36.6±13.4	40.2±12.5	0.004
	FAS	44.1±15.1	44.4±12.9	0.873
	Forward Digits	33.8±15.9	33.8±17.4	0.992
	Backward Digits	39.5±8.6	44.2±12.6	0.022
	COWAT	41.5±7.3	42.0±8.1	0.643
	Stroop Inhibition	37.6±11.4	40.1±11.0	0.031
	WCST Percent Errors	37.1±13.5	44.9±8.3	0.007
	WCST Perseverations	41.7±11.1	47.8±12.7	0.010
AVLT	Recognition Memory	35.6±16.5	43.4±15.7	0.011
	Total Learning Memory	32.9±8.6	36.5±11.9	0.036

SDMT, Symbol Digits Modalities test; FAS, Verbal Fluency test; COWAT, Controlled Oral Word Association test; WCST, Wisconsin Card Sorting Task. AVLT: Auditory Verbal Learning Test.
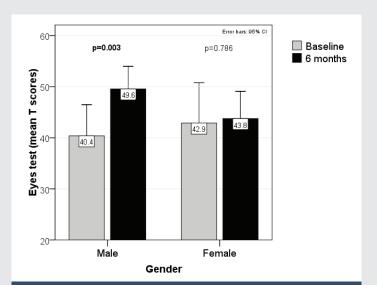

Figure 2: Mean scores and 95% confidence intervals in males and females in Eyes test tasks at baseline and at 6 months of ESL treatment. Males experienced a significant improvement, whereas the scores in females showed no significant changes.

Discussion

Epilepsy has a significant impact on cognition and psychological well-being. There is increasing evidence that ToM is impaired in patients with epilepsy [5]. Several studies have analyzed the impact of recurrent seizures and AED use on cognitive function [5,10,15], and it is reported that long-term AED treatment is associated with inattention and problems with working memory and verbal skills [10]. Nonetheless, our results indicate that ESL treatment may have a positive influence on social cognition and prefrontal cognitive functions in patients with focal onset epilepsy.

All our patients were adults with partial onset seizures diagnosed in adulthood and no active psychiatric comorbidities or cognitive dysfunction. Since ToM develops during childhood and early adolescence [3], we believe that any ToM impairment in these patients would likely be caused by the etiology of epilepsy, the seizures that occur, or the AED treatment received. The incidence and type of drug-related adverse events recorded were in line with previous clinical reports, and no relevant drug-related psychiatric events were reported during the study [12]. Previous studies have described greater impairment of ToM abilities and prefrontal functions in patients with frontal and temporal lobe epilepsy [5]. In contrast to those results, all our patients had well-preserved ToM, and attentional and executive functions regardless of the location of the epileptogenic source, which may be related to the late onset of the disease.

Our study showed no differences in the baseline ToM status according to gender, location of the epileptogenic source, cognitive function status, or seizure type or frequency. Nor were there differences related to the reason for starting ESL treatment, the characteristics of the seizures, or the ESL dose in the follow-up evaluation.

Although our patients showed a tendency to improvements in all ToM tasks during the study, only the Eye test and Faux Pas Recognition results were significantly higher under ESL treatment. The more marked improvement in males than in females in the Eye test tasks and some cognitive functions was not related to a poorer performance of males in the baseline evaluation, and we found no other reasonable explanation for the differences. A study on ESL pharmacokinetics found slight differences in metabolism of the drug between genders, with faster clearance in females [12], but the available evidence does not suffice to elucidate why males showed a greater improvement than females in our study.

Several factors related to treatment have been suggested to explain the improvements in cognitive function in epilepsy patients, such as the control of seizures and absence of AED-related adverse events [13,15]. Nonetheless, the improvement in ToM tasks and attentional and executive functions in our patients was independent of the decrease in seizures or the presence of side effects. Rather than being an effect of ESL on cognition, we consider that these findings may be related to the selection criteria, which may have excluded more severely affected patients (as evidenced by the large percentage receiving monotherapy) together with the principles of rational prescription applied by the treating neurologists [15].

This exploratory study has several limitations. The absence of a relevant improvement in the patients' self-reported quality of life or mood assessment may have been biased by exclusion of patients with high-risk comorbidities that could affect quality of life [27] and a duration of follow-up that may have been

too short to enable detection of significant differences. The small cohort of patients, absence of psychiatric disorders, no randomized treatments, and lack of a control group are major limitations for obtaining definitive conclusions. However, it is extremely difficult to conduct double–blind, randomized psycho–cognitive studies in patients with epilepsy; hence, clinical data of this type can be of value.

Conclusions

ToM and prefrontal cognitive functions in patients with epilepsy can be modified through the use of various pharmacological approaches. Our results indicate the ESL may have a positive effect on social cognition, mainly in males and regardless of the degree of seizure control.

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