Neuropsychological effects of antiepileptic drugs (carbamazepine versus valproate) in adult males with epilepsy

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Introduction

Epilepsy is a common health problem. Seizures are only one aspect of epilepsy. Patients with epilepsy may experience cognitive and behavioral problems that may have a deleterious impact on patients' overall lives. Cognitive comorbidity associated with epilepsy has been confirmed in clinical, experimental, pathological, psychological, physiological and imaging studies. Epileptic patients may experience problems in various cognitive domains such as reduced intelligence, attention, problems in memory, language and frontal executive functions, despite the side or site of lesion. The association between epilepsy and poor cognitive performance, learning and long-term memory is correlated with a number of variables including genetics, basic brain lesion, site and side of structural brain lesion, and age at onset together with duration of
epilepsy, seizure frequency, adverse effects from antiepileptic medications and psychosocial variables.7–10

Antiepileptic drugs (AEDs) have both negative and positive effects on cognition and behavior.3 AEDs are able to improve cognition and behavior, which has been attributed to reduction of seizure activity, and modulating effect on neurotransmitters and their psychotrophic effect. AEDs reduce neuronal irritability and increase postsynaptic inhibition or alter synchronization of neural networks to decrease excessive neuronal excitability associated with seizure development and secondary spread of epileptic activity to the surrounding normal brain. However, excessive reduction of neuronal excitability may result in slowed motor and psychomotor speeds, and poor attention and memory processing, which are common side effects of sodium channel blockade and increasing GABAergic inhibitory activity.11–13

It is not surprising that patients with epilepsy are more susceptible to the adverse behavioral effects of AEDs than other populations, possibly due to the disease associated structural or functional changes that increase their risk of psychiatric disorders.

Aim of the work
This study aimed to evaluate the effect of conventional AEDs (carbamazepine [CBZ] and/or valproate [VPA]) on cognitive and behavioral functions in a group of adult epileptic males with generalized tonic–clonic convulsions and controlled (seizure free for \( \geq 1 \) year) on AEDs. Correlations between cognitive and behavioral functions and variables related to AEDs (dose, duration of treatment and number of utilized AEDs) were also determined.

Patients and methods
This study included 79 consecutive patients (range 18 to 45) with generalized tonic–clonic convulsions (grand mal epilepsy) recruited from the outpatient epilepsy clinic of Assuit University Hospital, Assiut, Egypt. Epilepsy type was defined according to the International League Against Epilepsy (1989).14 The protocol of the study was in conformity with ethical guidelines of Assiut University Hospital, Egypt and informed written consent was obtained from each participant. Included in this study were: a) newly diagnosed and untreated epileptic patients: these were patients with at least one seizure during the last 6 months and who had not received AEDs (n = 34); b) treated epileptic patients: these were patients on regular treatment with one (monotherapy) or combined (polytherapy) AEDs (total: n = 45; CBZ: n = 25; VPA: n = 13; CBZ + VPA: n = 7). AEDs were described according to the well-known guidelines and in recommended doses. All treated patients gave a history of compliance to AEDs. Compliance was confirmed by assessment of the serum drug level at least once during the period of the study. The serum levels of AEDs were determined in the therapeutic drug monitoring lab, Assiut University Hospital, Assiut Egypt, with the fluorescence polarization immunoassay system of Abbott (EPIA) using TD \( \times \) FLX apparatus (Abbott Lab, Wiesbaden, Germany), as described before.15 This study included 58 healthy males matched for age, sex, educational level and socioeconomic status as controls (Table1). Excluded from this study were a) patients with intelligence quotient (IQ) less than 70 assessed using Wechsler Adults Intelligence Scale-Revised;16 b) presence of history of head injury; c) patients with progressive central nervous system (CNS), psychiatric or systemic medical conditions that might affect cognitive or behavioral functions; and d) patients utilizing chronic medications other than AEDs. The demographic and clinical characteristics of the studied groups are summarized in Table 1.

All participants were subjected to:
1. Complete neurological, medical history and examination, and socioeconomic status scale assessment.17
2. Analysis of seizure history included: age at onset, duration of epilepsy, type and duration of AED(s) utilized and the degree patients’ control on AED(s). Only controlled patients on AEDs (seizure free for \( \geq 1 \) year) were included in this study.
3. Neuropsychological assessment
   (a) Assessment of cognition
   Cognition was assessed using the standardized and validated Arabic version of the Stanford-Binet Test (4th edition).18,19 The test consisted of 30 items ranging from the ability to touch one’s nose or ear when asked, to the ability to draw designs from memory and to define abstract concepts. The following items were tested and analyzed: total verbal reasoning, which was used to assess vocabulary, comprehension, absurdities and verbal relations; total nonverbal short-term memory, which tested memory for objects and bead memory; and total verbal short-term memory, which was used to assess memory for digits (forward and backward) and memory for sentences.
   (b) Behavioral assessment
   A standardized and validated Arabic versions of the Beck Depression Inventory,20,21 the Aggressive Behavior Scale (Verbal and Nonverbal)22,23 and Eysenck Personality Inventory24,25 were used for behavioral and emotional
assessed. The Beck Depression Inventory is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression. Its development marked a shift among health care professionals, who had until then viewed depression from a psychodynamic perspective, instead of it being rooted in the patient’s own thoughts. In its current version the questionnaire is designed for individuals aged 13 and over, and is composed of items related to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The Aggressive Behavior Scale is a 64-item scale with excellent reliability and validity. It is used to assess verbal (32 items) and nonverbal aggressions (32 items). It measures levels of self-esteem, disinhibited behavior, aggression against persons and animals, control of rage, and so on. The scoring for each item ranges from 1 to 4. Higher scores indicate higher levels of aggression. Eysenck Personality Inventory assesses neurosis, psychosis, extroversion–introversion, and lying. Neurosis is marked by excessive anxiety or apprehension that is not restricted to specific situations or objects, unlike anxiety experienced in threatening situations. Psychosis is a temporary mental state. A person experiences a psychotic state for a while, and then come out of it. Psychoticism focuses on the disturbances of such magnitude that there is personality disintegration and loss of contact with reality. Extraversion is marked by direction of attention and energy outward from the self. Lying is typically used to refer to deceptions in oral or written communication.

Procedure
Cognitive and behavioral assessment of the patients was done individually. Patients were divided into two smaller groups. The first subgroup completed the vocabulary, comprehension, absurdities, verbal relations, memory for objects, bead memory, memory for sentences, memory for numbers forward, and memory for numbers backward tests in that order. The second subgroup completed the same tests in reverse order. The aim of this counterbalance was to control the training variable in cognitive function. Behavioral assessment was completed in another session.

Statistical analysis
Descriptive statistics (mean, SD, and percentages) were calculated using the computer software package SPSS for Windows, Version 16. Results were analyzed using independent-sample t test that did not assume equal variances. One-way analysis of variance (ANOVA) was followed by a post hoc test (LSD). Correlation coefficients and multiple linear regression analysis were used to detect the impact of epilepsy and its treatment on cognition, mood, aggressive behavior, and personality traits. The significance level was set at a ≤0.05.

Results
Table 1 demonstrates the demographic and clinical characteristics of the studied groups. Tables 2 and 3 demonstrate the effect of AEDs on various cognitive and behavioral functions. Compared to matched control subjects, treated and untreated epileptic patients had poor performance in different cognitive and behavioral functions testing. However, treated patients

Table 1 Demographic and clinical characteristics of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 58)</th>
<th>Untreated (n = 34)</th>
<th>Treated (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>30.45 ± 7.56</td>
<td>28.09 ± 8.99</td>
<td>28.80 ± 7.69</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>10.20 ± 3.914</td>
<td>9.68 ± 3.96</td>
<td>9.53 ± 3.75</td>
</tr>
<tr>
<td>Number of years of education</td>
<td>9.03 ± 5.67</td>
<td>7.91 ± 4.33</td>
<td>9.04 ± 3.74</td>
</tr>
<tr>
<td>Intellignt quotient</td>
<td>85.72 ± 15.79</td>
<td>78.24 ± 20.13</td>
<td>88.13 ± 20.46</td>
</tr>
<tr>
<td>P value</td>
<td>–</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>–</td>
<td>11.35 ± 7.65</td>
<td>10.07 ± 6.59</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>–</td>
<td>5 (14.7%)</td>
<td>11 (24.4%)</td>
</tr>
<tr>
<td>History of febrile convulsions</td>
<td>2 (5.9%)</td>
<td>3 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Family history of cognitive decline</td>
<td>–</td>
<td>1 (3%)</td>
<td>3 (6.8%)</td>
</tr>
<tr>
<td>Duration of drug intake, years</td>
<td>–</td>
<td>–</td>
<td>8.54 ± 6.52</td>
</tr>
<tr>
<td>AEDs dose, mg/day</td>
<td>–</td>
<td>–</td>
<td>739.39 ± 289.33</td>
</tr>
<tr>
<td>CBZ</td>
<td>–</td>
<td>–</td>
<td>822.22 ± 298.14</td>
</tr>
<tr>
<td>VPA</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± SD, number (%).
Significance: between untreated and treated groups.
Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; VPA, valproate.
The potential for AEDs to adversely impact cognition and behavior is of significant concern as they are the major therapeutic modality for control of seizures. Even their modest effects can be of clinical significance and affect the patient's quality of life. In this study, we compared the results of other cognitive and behavioral functions testing of a group of adult patients who were newly diagnosed or did not ever received conventional AEDs (CBZ and VP A), with a group of epileptic patients on AEDs and a group of matched healthy subjects.

The results of this study indicate that patients on conventional AEDs are at increased risk for cognitive dysfunction. The dose of AEDs was significantly correlated with testing scores for neurosis, verbal aggression and nonverbal aggression (r = 0.307; P = 0.009), psychosis (r = 0.586; P = 0.0001) and total nonverbal short-term memory (r = 0.384; P = 0.000). The duration of AED intake was significantly associated with testing scores for memory of objects (r = 0.323; P = 0.036), total verbal short-term memory (r = -0.314; P = 0.036), total nonverbal short-term memory (r = -0.46; P = 0.0001) and the dose of the AEDs. The number of utilized antiepileptic medications was significantly correlated with testing scores for memory of objects, bead memory (r = -0.346; P = 0.020), Beck Depression Inventory (r = -0.346; P = 0.020), Beck Depression Inventory (r = 0.346; P = 0.024) but not associated with other cognitive or behavioral functions.

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Table 2 Comparison between different studied groups in cognitive functions

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 58)</th>
<th>Untreated (n = 34)</th>
<th>Treated (n = 45)</th>
<th>CBZ (n = 25)</th>
<th>VPA (n = 13)</th>
<th>Polytherapy (n = 7)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocabulary</td>
<td>27.68 ± 7.14</td>
<td>25.50 ± 6.13</td>
<td>25.57 ± 5.68</td>
<td>26.20 ± 6.37</td>
<td>24.54 ± 4.59</td>
<td>25.28 ± 5.34</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Absurdities</td>
<td>30.00 ± 6.12</td>
<td>18.65 ± 6.64</td>
<td>18.15 ± 5.51</td>
<td>17.08 ± 5.26</td>
<td>17.92 ± 6.41</td>
<td>22.42 ± 1.98</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total verbal reasoning</td>
<td>85.74 ± 21.28</td>
<td>76.94 ± 20.74</td>
<td>75.29 ± 18.052</td>
<td>73.96 ± 17.33</td>
<td>73.07 ± 20.36</td>
<td>84.14 ± 15.79</td>
<td>0.045</td>
<td>0.010</td>
<td>NS</td>
</tr>
<tr>
<td>Memory for objects</td>
<td>10.65 ± 7.36</td>
<td>5.74 ± 2.440</td>
<td>6.0 ± 2.39</td>
<td>6.08 ± 2.25</td>
<td>5.69 ± 2.39</td>
<td>6.28 ± 3.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Bead memory</td>
<td>21.43 ± 6.94</td>
<td>17.88 ± 7.42</td>
<td>18.0 ± 5.38</td>
<td>17.64 ± 5.05</td>
<td>17.76 ± 4.83</td>
<td>19.71 ± 7.69</td>
<td>0.014</td>
<td>0.010</td>
<td>NS</td>
</tr>
<tr>
<td>Total non verbal short-term memory</td>
<td>32.08 ± 13.41</td>
<td>23.62 ± 9.14</td>
<td>24.0 ± 7.11</td>
<td>23.72 ± 6.88</td>
<td>23.46 ± 5.79</td>
<td>26.00 ± 10.42</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Memory for digits forward</td>
<td>6.31 ± 2.16</td>
<td>5.24 ± 2.36</td>
<td>4.77 ± 2.09</td>
<td>4.68 ± 2.19</td>
<td>4.84 ± 1.81</td>
<td>5.00 ± 2.44</td>
<td>0.024</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Memory for digits backward</td>
<td>3.19 ± 2.32</td>
<td>2.15 ± 2.13</td>
<td>1.78 ± 1.50</td>
<td>1.68 ± 1.10</td>
<td>2.00 ± 1.82</td>
<td>1.71 ± 2.21</td>
<td>0.019</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Total verbal short-term memory</td>
<td>26.66 ± 8.86</td>
<td>22.88 ± 9.04</td>
<td>21.33 ± 5.88</td>
<td>20.88 ± 5.74</td>
<td>21.54 ± 5.66</td>
<td>22.57 ± 7.43</td>
<td>0.032</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>27.68 ± 7.14</td>
<td>25.50 ± 6.13</td>
<td>25.57 ± 5.68</td>
<td>26.20 ± 6.37</td>
<td>24.54 ± 4.59</td>
<td>25.28 ± 5.34</td>
<td>NS</td>
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</tr>
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<td>5.69 ± 2.39</td>
<td>6.28 ± 3.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: Data are expressed as mean ± SD.
P1: untreated vs controls; P2: treated vs controls; P3: treated vs untreated.
VPA vs CBZ.
Abbreviations: CBZ, carbamazepine; VPA, valproate.
Table 3 Comparison between different studied groups in mood, behavior and personality traits

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 58)</th>
<th>Untreated (n = 34)</th>
<th>Treated (n = 45)</th>
<th>CBZ (n = 25)</th>
<th>VPA (n = 13)</th>
<th>Polytherapy (n = 7)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck questionnaire</td>
<td>10.11 ± 4.97</td>
<td>15.82 ± 7.32</td>
<td>16.14 ± 6.85</td>
<td>15.37 ± 6.36</td>
<td>15.23 ± 7.72</td>
<td>20.56 ± 6.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal aggression test</td>
<td>47.90 ± 16.02</td>
<td>64.330 ± 14.48</td>
<td>68.76 ± 13.13</td>
<td>64.96 ± 10.65</td>
<td>72.92 ± 13.64</td>
<td>74.57 ± 17.33</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonverbal aggression test</td>
<td>44.24 ± 17.40</td>
<td>69.90 ± 16.41</td>
<td>66.67 ± 12.48</td>
<td>63.16 ± 9.96</td>
<td>70.07 ± 12.43</td>
<td>73.00 ± 17.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total aggression test</td>
<td>92.15 ± 30.47</td>
<td>134.24 ± 29.29</td>
<td>135.44 ± 24.62</td>
<td>128.12 ± 19.95</td>
<td>143.00 ± 23.82</td>
<td>147.57 ± 34.63</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Neurosis</td>
<td>5.01 ± 2.55</td>
<td>15.03 ± 3.62</td>
<td>16.22 ± 3.78</td>
<td>15.24 ± 4.02</td>
<td>17.69 ± 2.68</td>
<td>17.00 ± 4.00</td>
<td></td>
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</tr>
<tr>
<td>Extroversion</td>
<td>11.45 ± 2.84</td>
<td>12.11 ± 3.40</td>
<td>13.38 ± 5.30</td>
<td>13.56 ± 6.19</td>
<td>14.15 ± 3.28</td>
<td>11.28 ± 4.96</td>
<td>0.439</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>9.90 ± 2.99</td>
<td>7.97 ± 3.50</td>
<td>7.47 ± 4.76</td>
<td>7.44 ± 4.31</td>
<td>7.92 ± 6.18</td>
<td>6.71 ± 3.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>11.88 ± 4.35</td>
<td>13.67 ± 2.69</td>
<td>13.60 ± 3.61</td>
<td>13.72 ± 3.61</td>
<td>13.15 ± 3.64</td>
<td>14.00 ± 4.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± SD. P1: untreated vs controls; P2: treated vs controls; P3: treated vs untreated. *P < 0.05 vs CBZ.

Abbreviations: CBZ, carbamazepine; VPA, valproate.

Disclosures

The authors declare no conflicts of interest.

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