

Montreal Cognitive Assessment in cryptogenic epilepsy patients with normal Mini-Mental State Examination scores

Kanitpong Phabphal, Janyapon Kanjanasatien

Neurology Unit, Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

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ABSTRACT – This cross-sectional study examined the Montreal Cognitive Assessment (MoCA) performance in cryptogenic epileptic patients aged more than 15 years with normal global cognition according to the Mini-Mental State Examination (MMSE) score. We tested our hypothesis that the prevalence of mild cognitive impairment and associated patient correlation factors might be increased (score < 26) according to the MoCA, in spite of a normal MMSE score, and that cognitive impairment might occur in a range of domains of the MoCA. Eighty-five patients participated in this study. The mean MoCA score was 22.44 (\pm 4.32). In spite of a normal MMSE score, which was an inclusion criterion, cognitive impairment was detected in 60% patients based on the MoCA score. The variable that correlated with a higher risk of cognitive impairment was the number of antiepileptic drugs (polytherapy: OR 2.71; CI 1.03-7.15). The mean scores of visuospatial and executive function, naming ability, attention, language, abstraction, delayed recall and orientation among patients with mild cognitive impairment were significantly lower than those of patients with normal cognitive function. These findings suggest that mild cognitive impairment in cryptogenic epileptic patients is common. We suggest using MoCA as a screening test for patients with epilepsy.

Key words: epilepsy, Montreal Cognitive Assessment, cognitive

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures that bear neurobiological, cognitive, psychological, and social consequences (Fisher *et al.*, 2005). The majority of patients with epilepsy are more likely to suffer from impaired cognitive perfor-

mance when compared with age- and education-matched healthy controls. Problems of attention and memory have been estimated in about 30% of newly diagnosed epileptic patients with single or several seizures of cryptogenic origin (Kälviäinen *et al.*, 1992). It was recently reported by Taylor *et al.* that

Correspondence:

Kanitpong Phabphal
Neurology Unit,
Department of Medicine,
Faculty of Medicine,
Prince of Songkla University,
Hat Yai, Songkhla, Thailand 90110
<pkanitpo@medicine.psu.ac.th>

53.5% of newly diagnosed untreated patients with epilepsy had at least one abnormal score (> 2 standard deviations below the control mean) based on a psychological test battery, compared with 20.7% of healthy volunteers (Taylor *et al.*, 2010). The domains most affected were memory and psychomotor ability. Other studies have reported the effects of epilepsy on intelligence, language, attention, executive function and psychomotor speech (Hermann *et al.*, 2008; Cahn-Weiner *et al.*, 2009; Oddo *et al.*, 2003). The ideal instrument for screening of cognitive impairment would take less than 15 minutes to administer, be free of change, and detect multiple domains of cognition. The Mini-Mental State Examination (MMSE) is a widely used screening tool for detecting cognitive deficits, especially since it may be completed quickly and is user-friendly.

In epilepsy, the MMSE is used to detect cognitive impairment and determine the effects of antiepileptic drugs (Wu *et al.*, 2009; Huang *et al.*, 2005). The MMSE may not capture cognitive domains affected across a wide spectrum of cognitive impairment (Wind *et al.*, 1997). Neuropsychological testing, although the gold standard for measuring cognitive performance, is lengthy and requires expertise for administration and interpretation. The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening tool with high specificity and sensitivity for detecting mild cognitive impairment. Executive function, language abilities, and visuospatial processing are assessed more rigorously with the MoCA relative to the MMSE. Therefore, we conducted this study in order to evaluate the frequency and correlation factors of cognitive impairment using the MoCA in patients with cryptogenic epilepsy. These patients were *a priori* defined as normal according to the MMSE. We hypothesized that the prevalence of mild cognitive impairment and associated patient correlation factors might be increased in a substantial proportion of patients with cryptogenic epilepsy (score < 26) based on the MoCA, in spite of having a normal MMSE score, and that cognitive impairment would occur in a range of domains, including visuospatial and executive function, naming, attention, language, abstraction, delayed recall and orientation.

Methods

Subjects

The study population included subjects aged 15 years or older who were seen as outpatients at the general medical, neurological and epilepsy clinics in Songklanagarind Hospital, Prince of Songkla University,

between January 2008 and June 2010. Songklanagarind Hospital is a tertiary hospital that is both the largest and the only hospital with an associated medical school in Southern Thailand. Subjects were included who were diagnosed with cryptogenic epilepsy for at least one year, had no seizure activity or change in the AED dosage in the three months prior to the commencement of the study. Subjects were excluded if they had signs for depression, structural abnormality on magnetic resonance imaging (MRI), progressive neuropathological conditions, were on medication interfering with cognitive function other than antiepileptic drugs, had a history of status epilepticus, or had other characteristics significantly interfering with cognitive functions e.g. mental retardation, diabetes, thyroid disease, renal disease, liver disease, or a psychiatric disorder. The study was approved by the Faculty of Medicine, Prince of Songkla University Research Ethics Board.

Neuropsychological testing

The research staff were trained to administer the MoCA and MMSE in a counterbalanced fashion. The participants completed both scales in their original format. Cut-off scores of < 26 and 24 were used as values indicative of cognitive impairment. These cut-off scores were chosen based on the cut-off values in previous studies assessing cognitive performance (Folstein *et al.*, 1975).

Statistical analysis

All statistical procedures were performed using R 2.11.1 software and the Epicalc package (Chongsuvivatwong, 2010). Cognitive impairment was defined as a total score of less than 26 according to the MoCA and no cognitive impairment as a total score of 26 or greater, as exhibited by the general population. Group comparisons between impaired and unimpaired samples on MoCA subscores and domains were made using a two-sample t-test or the Man-Whitney U-test. The correlates of cognitive impairment variables were determined using logistic regression models. Each demographic and clinical variable was analysed for marginal association with cognitive impairment using univariate logistic regression based on the p value. Variables were entered into a single, multivariate, logistic regression model with the backward stepwise entry method, and results were verified using the forced-entry method. For all other analyses, the Bonferroni correction for multiple comparisons was used to maintain at least a 0.05-significance level.

Results

Patient characteristics

Eighty-five patients (31 male, 54 female) participated in this study (table 1). All had normal MMSE scores. The mean age and age at onset (\pm standard deviation) was 32.32 (\pm 11.34) and 20.84 (\pm 12.72) years, respectively. The mean disease duration was 11.48 (\pm 9.22) years. There were 47 patients with disease duration of \leq 10 years. Concerning the education level, 41 patients had a high school diploma, 22 patients had a bachelor's degree, 15 had only finished primary school, two held a degree higher than a bachelor's degree and five patients were still studying at high school. Forty-four patients were receiving polytherapy and 41 monotherapy. All of our patients complained of cognitive problems and difficulties carrying out normal activities of daily living.

The mean MMSE score was 26.09 (\pm 3.19; range 19 to 30) and the mean MoCA score was 22.44 (\pm 4.32; range 11 to 30). In spite of a normal MMSE score, which was an inclusion criterion, cognitive impairment was detected in 60% based on a MoCA score of $<$ 26 (table 1).

Performance of Montreal Cognitive Assessment (MoCA) subdomains based on cognitive impairment

The mean score of visuospatial and executive function (\pm standard deviation) was 3.43 (\pm 1.50) in patients with cognitive impairment, which was significantly lower than that in people with normal cognition (4.53 [\pm 0.71]), $p = 0.00$. The mean scores of visuospatial and executive function, naming, attention, language, abstraction, delayed recall and orientation were 3.43 (\pm 1.50), 2.51 (\pm 0.70), 4.27 (\pm 1.30), 0.71 (\pm 0.97), 0.49 (\pm 0.73), 2.57 (\pm 1.65), 5.73 (\pm 0.64), respectively and were also significantly lower than those in patients with normal cognition whose mean scores were 4.53 (\pm 0.71), 2.94 (\pm 0.24), 5.56 (\pm 0.75), 1.97 (\pm 0.83), 1.35 (\pm 0.81), 3.94 (\pm 1.01), 6.00 (\pm 0.00), respectively ($p = 0.000, 0.001, 0.000, 0.00, 0.00, 0.00, 0.06$, respectively) (table 2).

Factors correlating with cognitive impairment

Among patients with cryptogenic epilepsy, the variable which correlated with a higher risk of cognitive impairment when the multivariate logistic regression models were adjusted for multiple comparison was the number of antiepileptic drugs (polytherapy: OR 2.71; CI 1.03-7.15) (table 3). Age ($>$ 30 years and $<$ 30 years), age at onset, and disease duration (\leq 10 years and $>$ 10 years) did not correlate with cognitive impairment based on univariate analysis (table 3).

Discussion

In cryptogenic epilepsy, no organic lesion is identified. The education level of our patients consisted of a bachelor's degree or higher in 24 of 85 patients (28.3%), a high school diploma in 48.2%, primary school level in 17.6% and 5.9% of the participants were still students. Standardised cognitive tests such as the Mini-Mental State Examination (MMSE) have been developed to streamline screening for cognitive impairment and decline. Ceiling effects and lack of adequate sampling of various cognitive domains in testing paradigms limit the sensitivity of these instruments for detecting cognitive impairment. High MMSE scores have been reported in individuals with well-ascertained dementia.

To the authors' knowledge, this is the first study on the use of a cognitive screening instrument in a cohort of patients with epilepsy who were shown to have normal global cognition based on the results of a commonly used standardised cognitive screening instrument (MMSE). The MoCA was designed to be more sensitive to abnormal performance across multiple domains such as visuospatial and executive function, naming, attention, language, abstraction, delayed recall and orientation in mildly impaired individuals (Nasreddine *et al.*, 2005). Two possible explanations can be given as to why the MoCA was more sensitive than the MMSE in detecting mild cognitive impairment in epileptic patients. Firstly, the MMSE instrument tests primary memory and language abilities, whereas the MoCA instrument tests a broader range of cognitive domains. Therefore, the MoCA score is likely to be more sensitive than the MMSE in detecting mild cognitive impairment in epileptic patients. Secondly, overall, the MoCA is more difficult than the MMSE, so it may be more sensitive to changes within a particular domain. Because the MMSE remains the most commonly used screening instrument for cognitive impairment in general, these results also suggest that the earliest stages of cognitive impairment in epilepsy often go unrecognised in routine clinical care. In spite of having normal MMSE scores, 60% of the patients met the criteria for cognitive impairment based on their MoCA scores. It has been estimated that the problems of attention and memory are observable in about 30% of cryptogenic epileptic patients with single or several seizures (Kälviäinen *et al.*, 1992). Huang *et al.* (2005) evaluated cognition using the Cognitive Ability Screening Instrument (CASI) and found 36% of cryptogenic epileptic patients to have cognitive impairment. This also reflects the cognitive reserve theory, which maintains that patients with greater cognitive reserve capacity tend to be able to sustain more neurobiological insults such as epileptic

Table 1. Subject characteristics of the original sample of 85 patients.

Variable	N (%) Mean \pm Standard Deviation
Age	32.32 \pm 11.34
< 30 years	40 (47.1)
\geq 30 years	45 (52.9)
Seizure type (partial epilepsy)	85 (100%)
Frontal lobe seizures	3 (3.6%)
Normal MoCA (n)	1
Abnormal MoCA (n)	2
Temporal lobe seizures	78 (91.8%)
Normal MoCA (n)	28
Abnormal MoCA (n)	50
Parietal lobe seizures	2 (2.3%)
Normal MoCA (n)	2
Abnormal MoCA (n)	0
Occipital lobe seizures	2 (2.3%)
Normal MoCA (n)	2
Abnormal MoCA (n)	0
EEG (interictal EEG)	
Epileptiform discharge	42 (49.4%)
No epileptiform discharge	43 (50.5%)
Number of seizures in the past year*	
No seizure activity	57 (67.1%)
Seizure activity 1-5	23 (27.1%)
Seizure activity > 5-10	4 (4.7%)
Seizure activity > 10	1 (1.1%)
Age at onset	20.84 \pm 12.72
< 20 years	46 (54.1)
\geq 20 years	39 (45.9)
Disease duration	11.48 \pm 9.22
\leq 10 years	47 (55.3)
> 10 years	38 (44.7)

Variable	N (%) Mean \pm Standard Deviation
Sex	
Male	31 (36.5)
Female	54 (63.5)
Education	
Still studying at high school	5 (5.9)
Completed primary school	15 (17.6)
High school diploma	41 (48.2)
Bachelor's degree	22 (25.9)
Higher than a bachelor's degree	2 (2.4)
Occupation	
Unemployed	18 (21.2)
Employed	15 (17.6)
Studying	24 (28.2)
Farming	13 (15.3)
Government/State enterprise	12 (14.1)
Commercial	3 (3.5)
AEDs	
Monotherapy	41 (48.2)
Polytherapy	44 (51.8)
TMSE	26.09 \pm 3.19
Normal	85 (100)
Abnormal	0 (0)
MoCA	22.44 \pm 4.32
Normal	34 (40.0)
Abnormal	51 (60.0)

*No seizure activity during the three months before the study period.

Table 2. Performance of Montreal Cognitive Assessment (MoCA) subtest based on cognitive impairment status (n = 85).

MoCA Subtest	Mean ± Standard Deviation		P-Value
	Cognitively Impaired (MoCA < 26) (n = 51)	Cognitively Unimpaired (MoCA ≥ 26) (n = 34)	
Visuospatial and executive	3.43 ± 1.50	4.53 ± 0.71	0.000
Naming	2.51 ± 0.70	2.94 ± 0.24	0.001
Attention	4.27 ± 1.30	5.56 ± 0.75	0.000
Language	0.71 ± 0.97	1.97 ± 0.83	0.000
Abstraction	0.49 ± 0.73	1.35 ± 0.81	0.000
Delayed recall	2.57 ± 1.65	3.94 ± 1.01	0.000
Orientation	5.73 ± 0.64	6.00 ± 0.00	0.006

*Mann-Whitney U-test

Table 3. Correlates of cognitive impairment based on an MoCA score < 26.

Variable	Odds Ratio (95% Confidence Interval)			
	Univariate Analysis	P-Value	Multivariate Analysis	P-Value
Age (years)				
>30 vs ≤ 30	0.60 (0.15-2.36)	0.454	-	-
Age at onset (years)				
>20 vs ≤ 20	3.30 (0.76-14.38)	0.103	2.60 (0.96-7.03)	0.06
Disease duration (years)				
>10 vs <10	0.72 (0.20-2.54)	0.608	-	-
Sex				
Female vs Male	1.17 (0.42-3.24)	0.765	-	-
Education				
Bachelor vs lower than bachelor	2.17 (0.72-6.52)	0.166	2.48 (0.85-7.26)	0.09
AEDs				
Monotherapy vs Polytherapy	2.36 (0.80-6.96)	0.118	2.71 (1.03-7.15)	0.04

seizures before manifesting cognitive symptoms than those with less cognitive reserve (Pai and Tsai, 2005; Bazan *et al.*, 2002).

The factor correlating to cognitive impairment was the number of antiepileptic drugs; polytherapy was related to cognitive impairment. In fact, it is well known that the complications of antiepileptic drugs may more often stem from the use of polytherapy than from the effects of an individual drug. In our study, which

was based on a cross-sectional design, only polytherapy correlated with cognitive impairment in the multivariate logistic regression analysis. This finding was in contrast with those from studies of Hamed (2009) and Hendriks *et al.* (2004). Earlier studies on the effects of antiepileptic drugs on cognitive function have revealed that tailoring therapy from polytherapy to monotherapy had a beneficial effect on cognition (Thompson and Trimble, 1981). A possible hypothesis

to explain the association between polytherapy and cognitive impairment is based firstly on the fact that pharmacodynamic interaction with deleterious effects on cognition is likely to occur during a polytherapy regimen. For example, two drugs with very mild cognitive effects which have no clinical significance may show potentiation of yield clinical significance when used in combination (Trimble, 1987). Secondly, it has been acknowledged that patients receiving polytherapy usually have chronic drug-resistant epilepsy, where cognitive deficits are likely to be present and, thus, more vulnerable to cognitive adverse effects of antiepileptic drugs. However, our subjects did not have seizure activity during the three months preceding the study and about one third had drug-resistant epilepsy (data not shown).

Furthermore, it should be taken into account that some antiepileptic drugs, such as phenytoin and phenobarbital, are reported to lead to metabolic change such as low serum, red blood cell and cerebrospinal fluid folate levels, particularly in polytherapy regimens (Reynolds, 1976). It is known that folic acid plays a role in several important central nervous system transmethylation reactions and is linked to monoamine metabolism. It has been suggested that some cases of encephalopathy with cognitive deterioration seen in clinical practice may be linked to the negative effect of antiepileptic drugs on serum folate levels which results in hyperhomocysteinaemia. Huemer *et al.* (2005) have studied epileptic patients receiving long-term antiepileptic drug treatment and found that the long duration of therapy enhances the risk for hyperhomocysteinaemia. Furthermore, they discovered that folic acid supplementation significantly reduced the risk of hyperhomocysteinaemia (Huemer *et al.*, 2005). However, all the patients in our study were taking folic acid during the course of this investigation; therefore, folate deficiency may have not played a major role in their cognitive impairment.

Most of the more recent antiepileptic drugs are generally not associated with significant cognitive effects in studies using neuropsychological tests (Hamed, 2009). Although there is scientific evidence to differentiate between different effects of individual antiepileptic drugs, definitive conclusions are lacking due to the multifactorial nature of association (Mula and Trimble, 2009). Antiepileptic drugs, especially benzodiazepine, barbiturates, and valproate, which are positive allosteric modulators of GABA neurotransmission, sodium channel blockers carbamazepine and phenytoin, as well as other new antiepileptic drugs such as topiramate, produce adverse cognitive effects of different degree. Even the magnitude of effect from each antiepileptic drug is difficult to determine because the majority of studies are either open label, have inadequate sample size, lack random assignment,

or fail to include appropriate controls. In addition to these methodological limitations, the duration of these studies is insufficient to determine the long-term cumulative effects of antiepileptic treatment on cognition (Loring and Meador, 2004; Park and Knon, 2008; Hamed, 2009; Ortinski and Meador, 2004). To the best of our knowledge, no studies combining new and old antiepileptic drugs have been carried out.

This study demonstrated a high prevalence of mild cognitive impairment and a clear correlation between polytherapy and mild cognitive impairment in cryptogenic epileptic patients. Also, significantly lower MoCA subscores were observed in patients with mild cognitive impairment than with normal cognitive ability. However, this study has some limitations; first, this is a cross-sectional study design, second, this study had a small sample size and third, temporal lobe epilepsy was not distinguished from other epilepsy types. Previous studies have demonstrated that both frontal lobe (Culhane-Shelburne *et al.*, 2002) and temporal lobe epilepsy (Baxendale *et al.*, 2010) result in cognitive deficits. This study included patients with frontal and temporal lobe epilepsy, who accounted for more than 95% of the total number. Lastly, epilepsy affects patients of all ages. Most neuropsychological studies involving MoCA are age-specific. Thus, it is very difficult to design appropriate neuropsychological testing for all age groups. However, the MoCA can be coded according to the specific level of education. The scoring of the MoCA test was adjusted according to years of education. If patients had less than 13 years of education, we added 1 point to the final score. Our study used 12 years of education as a covariate in all analysis. With reference to further study, we suggest a larger sample size in order to evaluate the effects on cognitive function between a combination of: 1) old and new drugs, 2) old drugs (enzyme inducer and enzyme inhibitor), and 3) new drugs.

Further studies comparing MoCA results and battery neuropsychological testing, especially the Alzheimer's Disease Assessment Scale-cognitive portion (ADAS-Cog), the ADCS Clinical Global Impression of Change (ADAS-CGIC), the ADCS Activities of Daily Living (ADAS-ADL), the Neuropsychiatric Inventory (NPI), the Clinical dementia rating scale (CDR), the Free and Cued Selective Reminding Test (FCSRT), the Delayed Matching to Sample (DMS)-48 visual memory test, the Stroop test, a verbal fluency test, the Trial Making Test, and the Frontal Assessment Battery are required to better understand the topic at hand.

Conclusion

Cryptogenic epilepsy is characterised by a high prevalence of mild cognitive impairment. The number of

antiepileptic drugs is the factor that best correlates with mild cognitive impairment and all MoCA sub-domains are lower in patients with cognitive impairment compared to their healthy counterparts. Adequate treatment of epilepsy should therefore not focus on seizure control alone. Screening for cognitive impairment is of great significance for patients with cryptogenic epilepsy, and prompt treatment is the best practice for care. □

Disclosure.

None of the authors has any conflict of interest to disclose.

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