DIAGNOSTIC VALUE OF MODIFIED MINI MENTAL STATE EXAMINATION FOR DETECTION OF COGNITIVE IMPAIRMENT IN CHILDREN WITH EPILEPSY

By

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ABSTRACT

Background: *Cognitive impairments are common in children with epilepsy not only in children with refractory epilepsy or with remote symptomatic causes but idiopathic and benign epilepsies may also lead to impairments in several domains of cognitive functions. Psychometric tests as Stanford-Binet test and Wechsler Intelligence Scale for Children (WISC) take a long time to administer, are expensive and need a well-trained psychologist, so a simpler screening test is needed in children with epilepsy.*

Objective: *Assessment of modified mini mental state examination (modified MMSE) as rapid diagnostic tool for detection of cognitive impairment in children with epilepsy aged from 6 to 12 years.*

Methods: *This cross-sectional comparative study was conducted in pediatric neurology outpatient clinic of El-Hussein University Hospital, Cairo, Egypt during the period from May 2019 to April 2020 and included 56 children aged 6 to 12 years with epilepsy. They were selected by simple random method. All subjects were evaluated for cognitive impairment using the Modified MMSE and then re-evaluated by a gold-standard cognitive evaluation test using the Stanford-Binet Intelligence Scales, Fifth Edition administered by a psychologist.*

Results: *In our study, the prevalence of cognitive impairment in children with epilepsy aged from 6 to 12 years was 57.14% (32 out of 56 patients) identified by Modified MMSE and it was 58.92% identified by Stanford Benet test (33 out of 56 patients) with no statistically significant difference. The highest mean of MMSE cognitive domains was for languages (9.0 ± 1.66) then orientation (5.83 ± 2.98) while the lowest domain was for recall (2.33 ± 0.84). Modified MMSE had a sensitivity of 93.93%, specificity of 95.65%, an accuracy of 94.94%, positive predictive value of 96.87%, and negative predictive value of 91.66%.*

Conclusions: *Cognitive impairment is common in children with epilepsy. Modified MMSE is a rapid and valid diagnostic test, so it may be useful for detection of cognitive impairment in children with epilepsy.*

Key words: *Modified MMSE, epilepsy, cognitive function, cognitive impairment.*

INTRODUCTION

Cognitive impairments are common in children with epilepsy. They may already be present before the onset of epilepsy or occur and even progress during its course **[Nickels et al., 2016]**.

Prevalence of cognitive impairment and developmental delay in children with epilepsy in different studies vary largely and depend on many factors, including outcome definition, cohort selection, geography, and time since onset of seizures **[Aaberg et al., 2016]**. Variables that determine cognitive functioning are the underlying epileptogenic pathology, the presence of an epileptic encephalopathy, the burden of frequent seizures; interictal epileptiform EEG discharges (IEDs), the use of AEDs, and the surgical treatment of focal epilepsy **[Reilly et al., 2015]**.

Cognitive impairments are not restricted to children with refractory epilepsy or with remote symptomatic causes. Idiopathic generalized epilepsies and benign rolandic epilepsy may also lead to impairments in intellectual function **[Garcia-Ramos et al., 2015]**.

The presence of cognitive impairment has a significant effect on the quality of life for children with epilepsy through its impact on learning and social skills **[Besag, 2006]**.

There are numerous neuropsychological batteries used to assess children's cognitive function **[Nelson and Fischer, 2007]**. These batteries usually are domain specific and require trained professionals for their application and long application times. There is a need for simple cognitive screening tests for the assessment of different cognitive domains in a short time. So it could be a routine procedure, assisting in early detection of cognitive impairments **[Moura et al., 2017]**.

The Mini-Mental State Examination (MMSE) was developed by Folstein and associates as a brief standardized screening test for the assessment of the cognitive function in adults. The MMSE is composed of 11 items covering a wide range of cognitive domains, such as time and place orientation, immediate and short-term recall, attention, language functions, and constructional ability. These variables give a total score. Its administration takes about 5 to 10 minutes **[Blesa et al., 2001]**.

In the study conducted by **Jain and Passi, 2005**, a child-adapted MMSE showed brief

implementation (5-7 minutes) in age ranges from 3 to 14 years. Modified pediatric MMSE have been used in many studies, all suggest that it is a useful rapid assessment tool for cognitive impairment in children. **[Ouvrier et al., 1993**; **Besson and Labbé et al., 1997**; **Imam et al., 2002**; **Rubial-Álvarez et al., 2007**; **Andrade et al., 2011**; **Andrade et al., 2012]**. The modified MMSE is a suitable instrument for screening higher mental function in children at the age of 4 years and above and can be readily incorporated into the routine neurologic examination of children **[Ouvrier et al., 1993]**.

The Stanford-Binet Intelligence Scales, Fifth Edition (SB5) is an individually administered measure of intelligence and cognitive abilities for persons 2–85 years and older. The SB5 is used to diagnose a wide variety of developmental disabilities and can be used as part of early childhood assessment, psychoeducational evaluations for special education services, and for later career development planning. It was the first test to describe the term intelligence quotient by calculating the ratio of a person's mental age (based on test performance) divided by chronological age and multiplied by 100 **[Roid, 2003]**.

We aimed to assess the modified MMSE as rapid diagnostic tool for detection of cognitive impairment in children with epilepsy aged from 6 to 12 years

PATIENTS AND METHODS

Study design:

This was a cross-sectional comparative study conducted in pediatric neurology outpatient clinic of El-Hussein University Hospital, Cairo, Egypt during the period from May 2019 to April 2020.

Sample size calculation:

The minimum sample size required was 51 patients based on the following formula: n= (z2) P(100–P)/d2

Where n= sample size, z= z statistic for the level of confidence (for conventional 95% confidence interval, z value is 1.96, since 95% of a normal distribution would lie within ± 1.96 standard deviations on either side of the mean), P= expected prevalence of cognitive impairment among children aged 6 – 12 years with epilepsy (assumed as 74.29% based on **Lagunju et al., 2016** study and d= margin of error (set as 12%).

Ethical consideration:

1. Approval of ethical committee, Faculty of Medicine Al-Azhar University.
2. Written consents from parents of the patients.
3. The patients have the right to withdraw from the study at any time.
4. All the obtained data are confidential, and the patients have the right to keep them.
5. The authors declare that there is no any financial support regarding the research and publication.
6. No conflict of interest regarding the study and publication.

Inclusion criteria:

- Age and gender: children 6 to 12 years and of both genders.
- Children with epilepsy (diagnosed clinically and by electroencephalogram (EEG).
- Duration of epilepsy at least 6 months.

Exclusion criteria:

1. Age < 6years.
2. Children with visual impairment and/or severe hearing loss.
3. Uncontrolled epilepsy and patients who had seizures within one day of the examination.
4. Duration of epilepsy less than 6 months.
5. Those that couldn't complete the modified MMSE (uncooperative).
6. Patients with comorbidities affecting cognitive function, such as cerebral palsy, metabolic and genetic syndromes.

Methods:

All patients were subjected to the following:

1. History taking with stress on age of onset of epilepsy, epilepsy control (frequency and severity of seizures), sleep disorders and school performance.
2. Complete clinical examination with stress on neurological examination, neurocuteneous stigmata, dysmorphic features and anthropometric measurements.
3. Evaluation of cognitive function using the Modified MMSE. The Modified MMSE consists of seven cognitive domains: orientation, registration, attention and calculation, recall, language, and visuospatial function **(table below)**. In children aged

6-12 years, Modified MMSE had a total score of 37 and it had been administered by the authors. Children with scores below 26 were considered to have cognitive impairment.

4. Re-evaluation of cognitive function for confirmation of cognitive impairment using the Stanford-Binet Intelligence Scales, Fifth Edition administered by a psychologist.

Statistical analysis:

Our results were statistically analyzed by using the SPSS computer package version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp., USA). The mean ± SD were used for quantitative variables while number and percent were used for qualitative variables. We used a 2x2 table of the results of both Modified MMSE and Stanford-Binet tests to calculate the sensitivity, specificity, accuracy, and predictive values of Modified MMSE to diagnose cognitive impairment.

Modified MMSE for children [Ouvrier et al., 1993]

Function	Tests	Score
Orientation (total score = 12)	Name, surname, age, sex	One point for each, total score 4
	Name of parents, state, city, place	One point for each, total score 4
	Day/ Date/ Month/ Year	One point for each, total score 4
Attention and Concentration (total score = 7)	Minimum of 2 and Maximum of 5 digits forward	One point for each, total score 4
	Minimum of 2 and Maximum of 4 digits backward	One point for each, total score 3
Registration & Sensory perception	Identify 3 objects by name as Pen, watch and glasses	One point for each, total score 3
Recall	Tell 3 objects presented previously	One point for each, total score 3
Language (total score = 12)		
Name Body Parts	Points to 5 body parts indicated by the examiner: hand, foot, knee, nose, ear	One point for each, total score 5
Command	Unwrap the toffee, give the wrapper to the doctor (Three Step) & then eat it	One point for each, total score 3
Repeat Sentence	No ifs, ands, or buts	total score 1
Reading	Reads his/ her name	Total score 1
Writing	Writes own name	Total score 1
Copy a design	"Copy the drawings. Do it as best you can" (Vertical line at age 3 years, cross at age 4 years, circle at age 5 years, square at age 6 years and diamond at age 7 years)	Total score 1
Total score (maximum = 37)		

RESULTS

Our result will be demonstrated in the following tables and figures.

Table (1): General characteristics of the studied patient

Characteristics		n =56 (%)
Gender	Male	32 (57.1)
	Female	24 (42.9)
Ag (years)	Mean ± SD	8.4 ± 1.5
	6-8 years	24 (42.9)
	> 8-10 years	25 (44.6)
	> 10-12 years	7 (12.5)
Age of onset of epilepsy	≤ 5 years	23 (41.1)
	> 5 years	33 (58.9)
Antiepileptic drugs therapy	Monotherapy	41 (73.2)
	Polytherapy	15 (26.8)

These table showed that the mean age of study patients were 8.4 ± 1.5 years ranged from 6 - 12 years, 57.1% of them were males, in more than half of them (58.9%) the age of onset of epilepsy was > 5years, and in 26.8% the treatment by multiple antiepileptic drugs was reported.

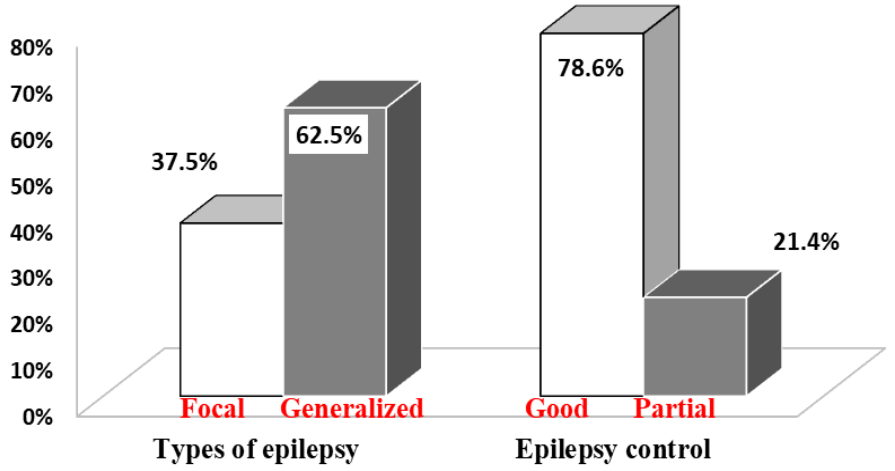

Figure (1): Types of epilepsy and its control among the studied patients.

This figure showed that generalized epilepsy was recorded in 62.5% and in majority of cases (78.6%) good control of epilepsy was noticed.

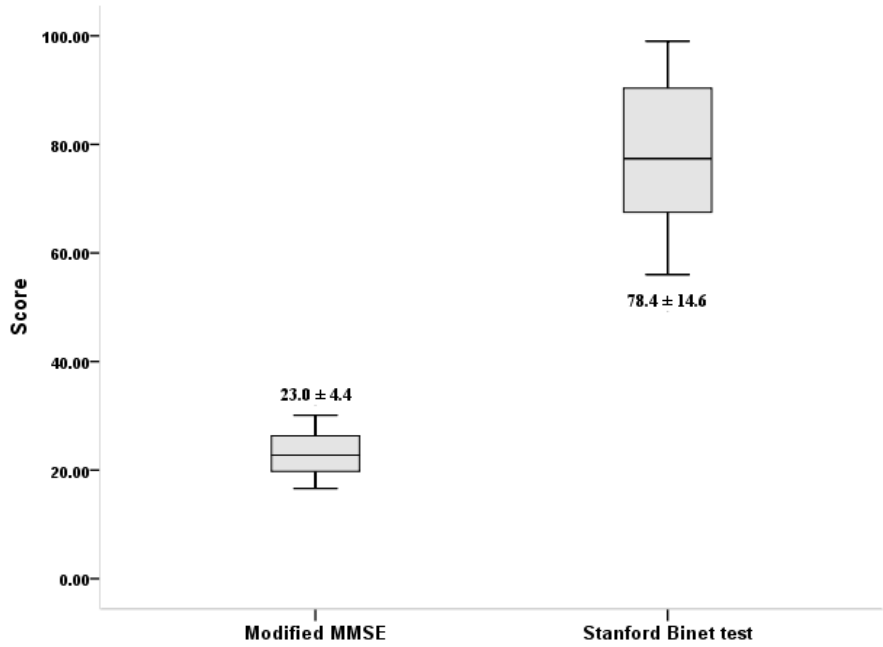

Figure (2): The total mean scores of Modified MMSE and Stanford Binet test

This figure show that the total mean score of modified MMSE was 23.0 ± 4.4 (out of 35) while the total mean score of Stanford Binet test was 78.4 ± 14.6 (reflecting low average to borderline impaired IQ).

Table (2): Prevalence of Cognitive Impairment in Studied Patients by Modified MMSE vs Stanford Binet test

Cognitive impairment	Test		P-value
	Modified MMSE n=56 (%)	Stanford Binet test n=56 (%)	
with cognitive impairment	32 (57.1)	33 (58.9)	1.000
without cognitive impairment	24 (42.9)	23 (41.1)	

This table showed that the prevalence of cognitive impairment diagnosed by Modified MMSE was 57.1% compared to 58.9% by Stanford Binet test with no significant difference between both tests.

Table (3): Modified MMSE results among the studied patients

Total Score	**N (%)**
Patients with cognitive impairment (score < 26)	32 (57.14)
Patients without cognitive impairment (score ≥ 26)	24 (42.86)
Sub-test results	**Mean ± SD**
Orientation	5.83 ± 2.98
Registration	3.11 ± 0.7
Attention & calculation	2.86 ± 2.93
Recall	2.33 ± 0.84
Language	9.0 ± 1.66

This table demonstrates that the prevalence of cognitive impairment among our patients was 57.14% (32 out of 56 patients) by using the Modified MMSE. The highest mean of MMSE cognitive domains was for language (9.0 ± 1.66) then orientation (5.83 ± 2.98) and the lowest domain was for recall (2.33 ± 0.84).

Table (4): Sensitivity, Specificity, Accuracy, Positive Predictive Value and Negative Predictive Value of Modified MMSE

	Confirmatory test (Stanford Binet test)		**Total**
Screening test (MMSE)	**with cognitive impairment**	**without cognitive impairment**	
with cognitive impairment	31	1	32
without cognitive impairment	2	22	24
Total	33	23	56

From this table Modified MMSE had a calculated sensitivity of 93.93%, specificity of 95.65%, an accuracy of 94.94%, positive predictive value of 96.87%, and negative predictive value of 91.66%.

DISCUSSION

The current study assessed the value of Modified MMSE in detection of cognitive impairment in children with epilepsy.

There was a slight male predominance of epilepsy in our study (57.1% were males), which was similarly reported by **Wanigasinghe J, et al., 2018**.

The age of onset of epilepsy in our study was > 5years, which is not the usual reported age of onset in other studies. **Wanigasinghe J, et al., 2018** reported highest prevalence of epilepsy in 0–5 age group and the prevalence seemed to decrease with advancing age. Also in a nationwide child cohort study, **Aaberg et al., 2017** found that the incidence rate of epilepsy was 144 per 100 000 person/years in the first year of life and 58 per 100 000 person/years through the following years up to age 10 years and the cumulative incidence was 0.45% at age 5 and 0.66% at age 10 years.

This is could be explained by our inclusion criteria that included only patients aged more than 6 years (mean age 8.4 ± 1.5) and many epilepsy remits before that age.

Similarly as we excluded patients with uncontrolled seizures, good control of epilepsy was noticed in 78.6% and only 26.8% of our patients treated by multiple antiepileptic drugs.

By using the Modified MMSE in our study, the prevalence of cognitive impairment among children aged 6 – 12 years with epilepsy was 57.14% (32 out of 56 patients) and by using Stanford Benet test it was 58.92% (33 out of 56). **Saputra et al., 2020** found cognitive impairment in 74.29% of children with epilepsy aged 8-11 years using the Modified MMSE. **Lagunju et al., 2016** also reported high prevalence of significant cognitive dysfunction in Nigerian children with newly diagnosed epilepsy, also using the Modified MMSE.

Guzeva et al., 2009 reported in their cohort of Russian children with epilepsy that intellectual-amnestic disorders were seen in 62% of children with epilepsy, more profound impairments being seen in patients with generalized epileptic seizures.

The highest mean of MMSE cognitive domains was for languages (9.0 ± 1.66) then orientation (5.83 ± 2.98) while the lowest domain was for recall (2.33 ± 0.84) Attention & calculation (2.86 ± 2.93). Similar results were reported by **Saputra et al., 2020** (the highest mean scores were language [mean 8.02 ± 1.66] and orientation [mean 6.23 ±2.95]. the attention and calculation sub-test had the lowest mean MMSE score [mean 3.44 ±3.13].

The explanation of this result could be the existing view that brain development during middle childhood is characterized by growth of the frontal lobe and maturation of the temporal lobe, these two structures play an

important role in the orientation and language processes. The dose and timing of stimulation given to a child determine whether the stimulus will be maintained as an experience. Such experiences play an important role in synaptogenesis. Adequate, repetitive, and consistent stimulation increases the branching of dendrites and proliferation and stabilization of synapses **[Thompson and Nelson, 2001**; **Perry, 2002**; **Casey, 2005** and **Schiller, 2010]**.

Calculation and backward spelling require more complex work and involve both cerebral hemispheres, especially in the counting process. Counting skills require a more complicated interaction between the language, visuospatial, and executive centers to maintain attention and working memory. These functions require communication between several brain areas, such as the dorsolateral prefrontal portion, the frontal lobe, the inferior parietal lobe, and the angular gyrus of the corpus callosum **[Thompson and Nelson, 2001**; **Perry, 2002**; **Casey, 2005**; **Lenroot and Giedd, 2006** and **Schiller, 2010]**. These reasons may explain the low sub-test score in attention and calculation in our subjects.

In our study, the Modified MMSE had a sensitivity of 93.93%, specificity of 95.65%, an accuracy of 94.94%, positive predictive value of 96.87%, and negative predictive value of 91.66%. These results suggest that Modified MMSE is potentially useful as a screening test for cognitive function abnormalities in children of this age group.

A meta-analysis of the diagnostic performance of MMSE in detecting dementia and mild cognitive impairment in primary care reported a sensitivity of 78.4% and specificity of 87.8% **[Mitchell, 2009]**. Another study which used MMSE to assess cognitive function in children aged 3-14 years with encephalopathy reported a sensitivity of 35% and specificity of 100%. Re-testing four days after the first administration showed a sensitivity of 68% and specificity of 100% **[Jain and Passi, 2005]**. Despite slight differences between different studies, all have reported that the Modified MMSE can be used as a screening tool to assess cognitive function in normal children, as well as in children with epilepsy.

Modified MMSE requires only 5-10 minutes to administer and can be done regularly in outpatient clinics with no additional cost,

while the Stanford Binet test may take up to 60 minutes with significant cost.

CONCLUSION

Cognitive impairment is common in children with epilepsy. The Modified MMSE has significantly high sensitivity and specificity to detect cognitive impairment in children aged 6 to 12years suffering from epilepsy, so, it may be used as a useful screening tool.

Recommendations:

We recommend application of Modified MMSE regularly in outpatient clinics for detection of cognitive impairment in children with epilepsy.

Study limitations:

The only limitation is that it was not a blind or randomized study.

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القيمة التشخيصية لفحص الحالة العقلية المصغر المعدل لكشف التدهور المعرفى لدى الأطفال المصابين بالصرع

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مقدمة: الإعاقات المعرفية شائعة عند الأطفال المصابين بالصرع، ليس فقط عند الأطفال المصابين بالصرع المقاوم للعلاج أو المصابين بالصرع نتيجة امراض اخرى ولكن الصرع مجهول السبب والصرع الحميد قد يؤدي أيضًا إلى ضعف في العديد من مجالات الوظائف المعرفية. الاختبارات النفسية مثل اختبار ستانفورد بينيه ومقياس ويكسلر تستغرق وقتًا طويلاً، وهي غالبا ما تكون مكلفة ماديا وتحتاج إلى اخصائى نفسي مدرب جيدًا، لذلك كانت هناك حاجه الى إجراء اختبار يكون أبسط للأطفال المصابين بالصرع.

الهدف: تقييم فحص الحالة العقلية المصغر المعدل كأداة تشخيصية سريعة لاكتشاف الضعف المعرفى لدى الأطفال المصابين بالصرع الذين تتراوح أعمارهم بين 6 و 12 سنة.

الطرق: أجريت هذه الدراسة في العيادة الخارجية لأمراض الأعصاب للأطفال بمستشفى الحسين الجامعي، القاهرة، مصر خلال الفترة من مايو 2019 إلى أبريل 2020، وشملت 56

طفلاً تتراوح أعمارهم بين 6 إلى 12 عامًا يعانون من الصرع. تم تقييم جميع الاطفال للضعف المعرفى باستخدام اختبار فحص الحالة العقلية المصغر المعدل ثم أعيد تقييمها من خلال مقاييس ستانفورد بينيه للذكاء، الإصدار الخامس وذلك بواسطة اخصائى نفسى.

النتائج: في دراستنا، كان معدل انتشار الضعف المعرفى لدى الأطفال المصابين بالصرع الذين تتراوح أعمارهم بين 6 و 12 عامًا هو 57.14٪ (32 من 56 مريضًا) تم تحديده بواسطة اختبارفحص الحالة العقلية المصغر المعدل وكان 58.92٪ حدده اختبار ستانفورد بينيت (33 من 56 مريضًا). كان أعلى متوسط للمجالات المعرفية للغة (9.0 ± 1.66) ثم الاتجاه (5.83 ± 2.98) بينما كان المجال الأدنى للتذكير (2.33 ± 0.84). كانت حساسية اختبارفحص الحالة العقلية المصغر المعدل 93.93٪، وخصوصية 95.65٪، ودقة 94.94٪، وقيمة تنبؤية إيجابية 96.87٪، وقيمة تنبؤية سلبية 91.66٪.

الخلاصة: ان اختبارفحص الحالة العقلية المصغر المعدل هو اختبار تشخيصي سريع وصالح، لذلك قد يكون مفيدًا للكشف عن ضعف الوظائف المعرفية لدى الأطفال المصابين بالصرع.