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Original Article

The School Years Screening Test for Evaluation of Mental Status-Revised (SYSTEMS-R) as a cognitive function screening tool in children with epilepsy

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Abstract

Background Children with epilepsy are at high risk of cognitive impairment that can affect quality of life. Intelligence quotient (IQ) measurement using the *Wechsler Intelligence Scale for Children* (WISC) is the gold standard test of cognitive function, but it is time-consuming and costly. *The School Years Screening Test for Evaluation of Mental Status-Revised* (SYSTEMS-R) is a potential cognitive function screening tool that can be used in children with epilepsy.

Objective To assess the performance of SYSTEMS-R as a cognitive function screening tool in children aged 6-15 years with epilepsy.

Methods This cross-sectional diagnostic test study was conducted in children aged 6-15 years with epilepsy. All subjects were assessed using both SYSTEMS-R and WISC 4th edition. The sensitivity, specificity, positive and negative predictive value, likelihood ratios of the positive and negative tests, and accuracy of SYSTEMS-R was calculated, with WISC as the gold standard test.

Results Based on the SYSTEMS-R, the prevalence of cognitive impairment in children aged 6-15 years with epilepsy in our population was 86.4%. With WISC as the gold SYSTEMS-R had 84% sensitivity, 91% specificity, 98% positive predictive value, and 47% negative predictive value. The likelihood ratio of a positive SYSTEMS-R test was 10.11 and the likelihood ratio of a negative test was 0.17. The overall accuracy of SYSTEMS-R ***to detect cognitive impairment was 85%.***

Conclusion SYSTEMS-R has good sensitivity and specificity to assess cognitive function in children 6-15 years with epilepsy. It can be considered for widespread use in the early detection of cognitive impairment in pediatric epilepsy patients aged 6-15 years. **[Paediatr Indones. 2024;64:377-83; DOI: https://doi.org/10.14238/pi64.5.2024.377-83**].

Keywords: *SYSTEMS-R; WISC; IQ; epilepsy; cognitive function*

Childhood is a period of rapid brain development, during which fundamental changes take place in the brain. At the cellular level, there is an increase in connections between neurons called synapses. This process, known as synaptogenesis, underlies the development of cognitive function in children. Cognitive development involves high-level brain functions, including learning and remembering, organizing, planning, solving problems, focusing, maintaining and shifting attention, and understanding language.[1]

Epilepsy is a chronic neurologic disease with a high incidence, especially in developing countries where health care systems have not successfully combated its causes, such as complications of pregnancy and childbirth, as well as infectious diseases. The incidence of epilepsy in children in developing countries is estimated to be around 40

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cases per 100,000 children per year.[1,2] Patients with epilepsy often experience cognitive impairment. The causes of cognitive impairment related to epilepsy are multifactorial, with complex interactions between seizures, age at onset, epileptogenic triggers, and antiepileptic drugs.[3,4]

The period between age 6 to 15 years describe early to middle childhood leading to adolescence. During this period, children are being formally educated, so they receive a large amount of new information, both on academic and non-academic matters.[5-7]Several instruments can be used to assess cognitive function in children. These instruments are usually specific for evaluating certain domains and require professional staff and a long time to process. In school-aged children, cognitive function assessed by evaluating their thinking ability according to age. *The Wechsler Intelligence Scale for Children* (WISC) has been widely used to assess intelligence quotient (IQ).[5,8]

The WISC examination is administered by a professional psychologist, requires time-intensive analysis of results, and is therefore quite costly.[9] Another instrument that has been developed to examine children's cognitive function is the *School-Years Screening Test for the Evaluation of Mental Status* (SYSTEMS). The SYSTEMS is a valid, reliable, and widely used cognitive function screening tool for children.[10,11] SYSTEMS was later revised into SYSTEMS-Revised (SYSTEMS-R), which has been validated for use in Indonesian children aged 4 to 15 years.[12] In 2019, age-specific standard reference values of SYSTEMS-R have been established through a study on 631 school children aged 4-15 years in Jakarta.[10]

Methods

This cross-sectional diagnostic test study was conducted in children aged 6-15 years with epilepsy who sought treatment at the Pediatric Neurology Outpatient Clinic of Dr. Cipto Mangunkusumo Hospital, Jakarta, from December 2019 to March 2020. Subejcts were recruited by consecutive sampling. The inclusion criteria were children aged 6-15 years who had been diagnosed with epilepsy, were cooperative, spoke Indonesian, and had parents or caregivers who spoke Indonesian. The participants' parents were asked to sign a written informed consent before their child was enrolled in the study. Exclusion criteria were the presence of severe visual and/or hearing impairments or comorbidities affecting cognitive impairment, such as severe cerebral palsy.

The socioeconomic status of participants was determined by their parents' monthly income based on Jakarta's monthly minimum wage. It was categorized as sufficient if their income was equal to the minimum wage or more and insufficient if their wage was less than the minimum wage. Parents' education level was determined the number of years of formal education and classified as moderate to high if it was >9 years and low if it was <9 years.

We recorded the participants' clinical history and performed general physical and neurological examination. We also obtained participants' clinical characteristics from their medical records, including age at onset, seizure semiology, seizure duration, seizure frequency, seizure control, antiepileptic drugs (AEDs) taken, and the duration for which the AEDs had been taken.

All subjects underwent both the SYSTEMS-R test, administered by the principal investigator, and WISC 4th edition, administered by a psychologist. We used age-specific norms for the Indonesian version of SYSTEMS-R.[12] SYSTEMS-R consists of 40 questions across 11 subtests: orientation, registration, attention, calculation, aditory recall, visual recall, short-term memory, long-term memory, language, executive function, and visuospatial. Each question was scored 1 if answered correctly and 0 if answered incorrectly. The sum of scores for all questions was calculated to obtain a total score, with a maximum of 40 points. Scores indicative of cognitive impairment were ≤7 for the age of 4 years, ≤13 for the age of 5 years, ≤18 for the age of 6 years, ≤19 for the age of 7 years, ≤22 for the age of 8 years, ≤27 for the age of 9 years (≤27), ≤28 for the age of 10 years, ≤29 for the age of 11 years (≤29), ≤30 for the age of 12-13 years, and ≤31 for the age of 14-15 years.10,11 The WISC 4th edition has 15 subtests, but only ten core subtests are commonly administered; the remaining five are considered supplementary subtests. The ten subtests measure four indices needed to compute the IQ: the verbal comprehension index (VCI) and the perceptual reasoning index (PRI) containing three subtests each, and the working memory index (WMI)

and the processing speed index (PSI) containing two subtests each. An IQ of ≤90 was indicative of cognitive impairment.[9]

Statistical analysis was done using *SPSS version 26* (*IBM*, Armonk, New York). We constructed 2x2 tables to compute the diagnostic sensitivity, specificity, positive and negative predictive values, and likelihood ratios of SYSTEMS-R, with WISC 4th edition as the gold standard test. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Results

Of 104 epilepsy patients aged 6-15 years seeking treatment at the Pediatric Neurology Outpatient Clinic of Dr. Cipto Mangunkusumo Hospital during the study period, 9 were excluded (8 with cerebral palsy and 1 with hearing loss). Ninety-five patients underwent SYSTEMS-R testing, but 7 of them did not return for WISC testing due to pandemic conditions. Thus, 88 research subjects were included in the study. **Table 1** shows their characteristics.

Based on WISC results, 76/88 (86.4%) children had cognitive impairment. On SYSTEMS-R testing, 65/88 (73.9%) children had cognitive impairment. The 65 subjects with cognitive impairment according to SYSTEMS-R mostly consisted of girls (35/65; 53.9%), age group >12-15 years (25/65; 38.5%), had an age of onset of <5 years (33/65; 50.8%), generalized seizures (42/65; 64.6%), non-intractable epilepsy (56/65; 86.2%), received polytherapy (42/65; 64.6%), and had taken AEDs for >6 months (60/65; 92.3%) (**Table 2**).

The SYSTEMS-R highest mean scores were in the attention [4.81 (SD 3.17)] and language [4.65 (SD1.81)] subtests, while the lowest subtest score was in executive function [0.07 (SD 0.33)] (**Table 3**). The mean WISC score was 67.8 (SD 20.84).

The 2x2 table of SYSTEMS-R compared to WISC as gold standard can be seen in **Table 4**. The diagnostic values of SYSTEMS-R to detect cognitive impairment in children 6-15 years with epilepsy are presented in Table 5. SYSTEMS-R was found to have

Table 1. Characteristics of study subjects

Characteristics	(N=88)
Sex, n (%)	
Male	43 (48.9)
Female	45 (51.1)
Age group, n (%)	
6-9 years	30 (34.1)
>9-12 years	30 (34.1)
>12-16 years	28 (31.8)
Onset of epilepsy, n (%)	
<5 years	42 (47.7)
≥5 years	46 (52.3)
Socioeconomic, n (%)	
Sufficient	39 (44.3)
Insufficient	49 (55.7)
Education, n (%)	
Enough	63 (71.6)
Low	25 (28.4)
Seizure type, n (%)	
Generalized	54 (61.4)
Focal	34 (38.6)
Intractable epilepsy, n (%)	
Yes	10 (11.4)
No	78 (88.6)
Number of AEDs, n (%)	
Polytherapy	47 (53.4)
Monotherapy	41 (46.6)
Duration of AED treatment, n(%)	
<6 months	7 (8.0)
≥6 months	81 (92.0)

Table 2. Characteristics of subjects with cognitive impairment according to SYSTEMS-R

Characteristics	(N=65)
Gender, n (%)	
Male	30 (46.1)
Female	35 (53.9)
Age group, n (%)	
6-9 years	19 (29.2)
>9-12 years	21 (32.3)
>12-16 years	25 (38.5)
Onset of epilepsy, n (%)	
<5 years	33 (50.8)
≥5 years	32 (49.2)
Seizure type, n (%)	
Generalized	42 (64.6)
Focal	23 (35.4)
Intractable epilepsy, n (%)	
Yes	9 (13.8)
No	56 (86.2)
Number of ASM, n (%)	
Polytherapy	42 (64.6)
Monotherapy	23 (35.4)
Duration of ASM, n (%)	
<6 months	5 (7.7)
≥6 months	60 (92.3)

84% sensitivity and 91% specificity to detect cognitive impairment in children with epilepsy aged 6-15 years.

Discussion

The prevalence of cognitive impairment in our study based on WISC, the gold standard test, was 86.4%. A previous study done in 2018-2019 in Jakarta, using the modified *Mini-Mental State Examination* (MMSE) found a prevalence of cognitive impairment of 72.9% among children 8-11 years old with epilepsy.[13] This might be due to the different population studied; our study was done in a national tertiary referral center in Jakarta, while the study by Saputra *et al.*[13] may have included patients with less complicated cases.

We found that most (64.6%) children with cognitive impairment received AED polytherapy. It has been previously noted that cognitive impairment is more prevalent in epilepsy patients using polytherapy.[14-18] Antiepileptic drugs can negatively affect cognitive and behavioral function by suppressing nervous excitability or increasing inhibitory neurotransmitters. The main cognitive effects of antiepileptic drugs are decreased attention, alertness, and critical thinking. Phenobarbital has the greatest effect on cognitive impairment, followed by valproic acid, carbamazepine, and phenytoin. Usually, a sustained effect is associated with high doses and the use of polytherapy, i.e., the use of ≥2 AEDs, each of which can cause cognitive impairment.[16,19,20]

In our study, the large majority of subjects (88.6%) had non-intractable epilepsy. Even though over half of the subjects (53.4%) received polytherapy, the number of subjects with intractable epilepsy was small (11.4%). This shows that it is possible for children with epilepsy to have good seizure control with more than one AED, usually on a submaximal dose. It also suggests that seizure control is strongly influenced by the choice of AED appropriate for the seizure type.

Table 3. SYSTEMS-R subtest scores of study subjects

Subtest		
SYSTEMS-R	Mean (SD)	Median (range)
Orientation	0.51 (0.50)	1 (0-1)
Registration	2.38 (1.12)	3 (0-3)
Attention	4.81 (3.17)	5 (0-10)
Calculation	0.68 (0.79)	0 (0-2)
Auditory recall	1.14 (1.16)	1(0-3)
Visual recall	1.47 (0.84)	2 (0-7)
Immediate memory	1.56 (0.78)	2 (0-3)
Long-term memory	0.84 (0.94)	0 (0-2)
Language	4.65 (1.81)	5 (0-7)
Executive function	0.07 (0.33)	0 (0-2)
Visuospatial	3.55 (1.89)	4 (0-5)

Normal: ≥ 0.07; below normal: <0.07

Table 4. Detection of cognitive impairment based on SYSTEMS-R *vs*.WISC

Cognitive impairment SYSTEMS-R	WISC		
	Yes	No	Total
Yes	64	1	65
No	12	11	23
Total	76	12	88

Table 5. SYSTEMS-R diagnostic values

Diagnostic measure	Value	95% CI
Sensitivity	84%	74.04 to 91.57
Specificity	91%	61.52 to 99.79
Positive predictive value	98%	90.72 to 99.76
Negative predictive value	47%	34.67 to 61.29
Positive likelihood ratio	10.11	1.54 to 66.16
Negative likelihood ratio	0.17	0.10 to 0.30
Accuracy	85%	76.06 to 91.89

The treatment plan for patients with cognitive impairment is to provide special therapy to optimize their capability to adapt and develop. These children are then advised to participate in special schools and receive counseling. The family system should also be evaluated to assess the effect of this cognitive impairment on the family.[10]

The highest mean SYSTEMS-R subtest scores in our subjects were attention [4.81 (SD 3.17)] and language [4.65 (SD 1.81)] (**Table 3**). This finding was in agreement with the theory that during middle childhood, brain development is characterized by the growth of a more specific structure, especially in the frontal lobe. Almost all parts of the temporal lobe mature at this age and are fully functioning, starting at the age of 4 to 8 years. Both the frontal and temporal lobes are important in the processes of attention and language. Attention is the result of interaction between the ascending reticular activating system (ARAS) in the brainstem, limbic system, superior parietal lobe, and dorsolateral prefrontal cortex. Subcortical structures that play a role in regulating these domains begin to develop when children are over one year of age. Language is a process of encoding and decoding semantic and syntactic components used in producing and understanding one's thoughts or ideas. Language function involves both hemispheres of the brain. The posterior superior temporal lobe area, called Wernicke's area, plays a role in understanding and forming language. The area inferior to the frontal lobe, known as Broca's area, plays a role in motor language.[10]

Maintaining a stimulus as an experience is dependent on the stimulus' volume and timing.[5] Experience has an important role in synaptogenesis, leading to more productive nerve cells and better and stronger connections between axons.[12] Adequate stimulation that is repeated and consistent increases dendritic branching, proliferation, and synapse stabilization.[21] In our study, the executive function subtest had the lowest score [0.07 (SD 0.33)]. This subtest consists of 3 questions with a maximum subtest score of 2. Questions in the form of proverb interpretation skills test abstract ability to explain similarities or interpret proverbs. The SYSTEMS-R examination is more complete when compared to other cognitive examinations such as the MMSE, which does not include an executive function subtest.[10] Executive function is a higher cognitive function, a set of cognitive abilities that control and regulate other abilities and behaviors, such as attention, memory, and organization. Given the complexity of executive function, it is understandable that the executive subtest score is the lowest in our study.

With WISC 4th edition as the gold standard cognitive function test, the SYSTEMS-R had 84% sensitivity and 91% specificity (**Tables 4** and **5**). The accuracy of SYSTEMS-R in determining cognitive impairment was 85%, also due to the high sensitivity and specificity in determining the impairment of cognitive function. SYSTEMS was first used in 1999 on 1,207 children in primary schools in Sydney and in hospitals in Westmead, Australia. The sensitivity and specificity of SYSTEMS in primary school children were 83% and 76%, respectively, and in hospitalized children were 92% and 95%, respectively. There was a strong correlation between SYSTEMS scores and mental age (r=0.88).[10]

SYSTEMS was originally an extension of the MMSE, a cognitive screening instrument for adults developed by Folstein in 1975.[10] The SYSTEMS was later redeveloped into SYSTEMS-R, with the aim to use it more widely in children aged 4 to 15 years.[10] Prior to our current study, research using SYSTEMS-R was geared at determining normal reference values in the school-aged population in Australia.[10,22] Likewise, previous studies using SYSTEMS-R in Indonesia have aimed to determine reference values in Indonesian schoolchildren.[11,23] One previous study that measured the cognitive function of children with epilepsy is the study by Saputra et al., which reported the sensitivity and specificity of the MMSE to be 83% and 85%, respectively, in detecting cognitive impairment in children aged 8-11 years with epilepsy.[13] Based on our findings, SYSTEMS-R had higher sensitivity and specificity and is applicable to a wider age group.

The positive predictive value and negative predictive value of SYSTEMS-R were 98% and 47%, respectively. Positive and negative predictive values change depending on the prevalence of the disorder. In our study, the prevalence of cognitive impairment from the WISC IQ examination was 86.4%, so a high positive predictive value was obtained. The low negative predictive value in our study could have been caused by the relatively high number of false

negatives on the examination using SYSTEMS-R. As such, in clinical practice, if a patient tests negative for cognitive impairment using SYSTEMS-R, clinical judgment should be the determining factor of whether cognitive impairment is, in fact, present. This predictive value is an unstable part of the diagnostic test, since it is affected by prevalence. The likelihood ratios of the positive and negative tests were 10.11 and 0.17, respectively. This positive likelihood ratio exceeded 10, which indicates a strong positive. In our study, values close to 0 indicate a strong negative likelihood ratio, so subjects with a negative diagnostic test (strong negative value on SYSTEMS-R) have only 0.17 times the odds of cognitive impairment. In our study, the SYSTEMS-R examination required an examination time of 10-15 minutes, slightly longer than that of the normal child population, who took 7-12 minutes.10 SYSTEMS-R can be performed by pediatricians, neurologists, and other health professionals to assess children with cognitive impairment, while the WISC examination takes 30-60 minutes and can only be performed by psychologists.[10]

In conclusion, the prevalence of cognitive impairment in children aged 6-15 years with epilepsy at Dr. Cipto Mangunkusumo Hospital, Jakarta, in 2019-2020 was 86.4%. SYSTEMS-R can be used as a screening tool for cognitive impairment in this age group, with a sensitivity of 84% and specificity of 91%.

Conflict of interest

None declared.

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