Does the Suzuki stage and symptom-related variables correlate with the neuropsychologic status?

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Directed by Professor Dong-Seok Kim

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ABSTRACT

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Objective: Because of repeated ischemic insults such as transient ischemic attack and/or cerebral infarction, intellectual development is impaired in a certain subgroup in pediatric age groups at the time of diagnosis. Several studies reported intellectual problems of pediatric moyamoya disease (MMD) patients. The purpose of this study was to evaluate the change of intellectual and neuropsychological profiles according to the angiographic alteration and symptom variables.

Methods: During the period from 2008 to 2009, presurgical neuropsychological assessments were done on forty-six children with neuroradiologically confirmed MMD. And also, thirty-four children in non-clinical normal control group, who were participating in separate studies that were conducted at the Department of Clinical psychology. Neuropsychological assessments included the intelligence, memory, attention, and executive function. Intelligence was evaluated with the Korean Wechsler Intelligence Scale for Children-Third Edition (K-WISC-Ⅲ). Memory was evaluated with the Rey-Kim Memory Test for children, which provides general memory quotient with the results from Auditory Verbal Learning test and Complex Figure Test. Measures of Attention

were obtained using Attention-Deficit Hyperactivity Disorder Diagnostic System. Executive Function was measured with Wisconsin Card Sorting Test.

Results: Normal control group showed better intelligence, memory and executive function than MMD patients (p-value < 0.05). However, attention such as inattention and impulsivity are no significant differences between two groups. In regards to Intelligence, the group classification by Suzuki stage in left sided hemisphere showed relatively more group differences. According to Matsushima classification, the Moyamoya group showed significant differences in Perceptual organization and Attention & Concentration amongst FSIQ, PIQ, and composite subtests in right sided hemisphere. Suzuki stage right 2 group demonstrated significantly higher MQ than Suzuki stage right 3 and 4, while the memory quotient of the group right 3 was higher than that of group right 4 but not to the significant level. With Executive Function, Suzuki stage left 1 group demonstrated better performances than Suzuki stage left 3 group in the rates of total errors and conceptualization.

Conclusion: Neuropsychological profiles showed that the classification by Suzuki stage is more sensitive to the decline of left hemisphere dominant functions and the Matsushima classification to the decline of right hemisphere dominant functions. In terms of symptom classification, the Moyamoya group with TIA maintained significantly better overall cognitive functions than the group with infarct with less attention problems.

Key words: moyamoya, psychological test, stage, transient ischemic attack

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I. INTRODUNCTION

Moyamoya disease (MMD) is a pathological condition characterized by bilateral progressive stenosis or occlusion at the terminal portion of the ICA with secondary formation of capillary network at the base of the brain[1]. It is well known that pediatric MMD patients develop transient ischemic attack (TIA) and/or cerebral infarction[2]. MMD in children mainly causes ischemic symptoms due to inadequate perfusion, whereas in adults hemorrhage. Previous reports have clarified that surgical revascularization such as indirect encephaloduroarterialsynangiosis (EDAS) and/or direct superficial artery to middle cerebral artery bypass can improve cerebral perfusion, thereby reducing the risk of ischemic insults and improving the activity of daily living in MMD patients. However, because of repeated ischemic insults such as TIA and/or cerebral infarction, intellectual development is impaired in a certain subgroup in pediatric age groups at the time of diagnosis. Several studies reported intellectual problems of pediatric MMD patients[3-8]. Neurocognitive problems are a critical factor in determining outcomes and quality of life. However, previous studies have not reported difference of

neurocognitive and psychological profiles according to angiographic staging and symptom variables. So, we have attempted to investigate whether MMD compromise neurocognitive function and neuropsychological profiles in pediatric patients and how to change according to the angiographic staging and symptom variables, we analyzed their neuropsychological functions using a variety of assessments.

II. MATERIALS AND METHODS

1. Patients Populations

During the period from 2008 to 2009, presurgical neuropsychological assessments were done on forty-six children (boys 21, girls 25, mean of age=8.04 years) with neuroradiologically confirmed MMD who attended the pediatric neurosurgery of Severance Children's Hospital, Seoul, Korea. We classified them into the Suzuki stage according to angiographic finding[9]. Suzuki stages of digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) of cerebral hemispheres were as follows; right sided Suzuki stage 1, 1; stage 2, 9; stage 3, 30; stage 4, 6; left sided Suzuki stage 1, 4; stage 2, 13; stage 3, 24; stage 4, 5. There are no stage 5 and 6 in both hemispheres. Symptom variables such as infarction, TIA, and/or hemorrhage were typed according to Matsushima classification[10]. Matsushima classification were as follows; right sided grade 2, 34; grade 3, 1; grade 4, 9; grade 5, 2; left sided grade 2, 33; grade 4, 10; grade 5, 3. There is no hemorrhagic presentation in both hemispheres.

Thirty-four children (boys 19, girls 10, mean of age=7.85 years) in non-clinical normal control group, who were participating in separate studies that were conducted at the Department of Clinical psychology in Yonsei University, completed the same battery of neuropsychological assessments.

2. Neuropsychological Assessment

Intelligence was evaluated with the Korean Wechsler Intelligence Scale for Children-Third Edition (K-WISC-Ⅲ) as it provided the level of general intelligence in terms of Full Scale intelligence quotient (IQ, FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ)[11]. The levels of composite scores such as Verbal Comprehension, Perceptual Organization, Concentration, Processing Speed as well as subtest scores including Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, and Picture Assembly were also considered.

Memory was evaluated with the Rey-Kim Memory Test for children, which provides general memory quotient with the results from Auditory Verbal Learning test and Complex Figure Test[12].

Measures of Attention were obtained using ADHD (Attention-Deficit Hyperactivity Disorder) Diagnostic System (ADS), which provides T-scores and qualitative description of Inattention, Impulsivity, and Standard Deviation of Reaction Time[13].

Executive Function was measured with Wisconsin Card Sorting Test (WCST), computerized version, which provides information on conceptual level responses, perseverative errors, nonperseverative errors, trials to 1st category, failure to maintain set, number of category completed and learning to learn[14].

3. Statistical analysis

Group differences were analyzed by SPSS software, 13.0 for Windows version (SPSS, Chicago, IL, USA). To examine differences in neuropsychological functions from Suzuki stage and Matsushima classification, ANOVA, two-way ANOVA and some descriptive statistics were used. All results are presented with 95% confidence intervals, and the threshold for statistical significance was at $p<0.05$.

III. RESULTS

During the period from 2008 to 2009, we evaluated neuropsychological test in 46 MMD patients and 34 normal control children. We compared cognitive function and neuropsychologic variables between MMD patients and normal control children. In the intelligence, normal control group showed better FSIQ, VIQ, PIQ, and other variables than MMD patients did. Memory and executive function were also significantly better in normal control group. There was no difference between boys and girls. However, attention such as inattention and impulsivity showed no significant differences between two groups (Table 1). About 30% of MMD patients were in below average or abnormal range of intelligence and memory function (FSIQ : 30.4%, VIQ : 19.6%, PIQ : 32.6%, and MQ : 32.3%). Also, about 50% of MMD patients appeared subnormal in attention and executive function except category completed ability (Table 2).

Table 1. Compare with Neuropsychological variables in Moyamoya Disease and normal control

	Moyamoya Disease	Normal Control	*P*-value
Intelligence			
FSIQ	86.67	110.03	0.000
VIQ	92.07	112.70	0.000
PIQ	80.71	103.91	0.000
Verbal comprehension	95.73	108.00	0.001
Perceptual organization	87.03	106.92	0.000
Concentration	84.30	111.92	0.000
Performance speed	93.93	104.70	0.019
Memory			
MQ	87.48	101.75	0.014
Attention			
Inattention	79.95	78.84	0.363
Impulsivity	85.84	66.58	0.118
Standard deviation of response time	87.32	73.16	0.264

Executive Function			
Category completed	26.20	50.00	0.006
Learning to learn	18.86	42.10	0.006

Table 2. Qualitative rate of abnormal range in Moyamoya Disease

		N (tot. N)	Mean(SD)	% in below average or abnormal range
Intelligence	Full Scale IQ	14 (46)	86.67	30.4
	Verbal IQ	9 (46)	92.07	19.6
	Performance IQ	15 (46)	80.72	32.6
Memory	MQ	10 (31)	87.48	32.3
Attention	Inattention	23 (38)	79.95	49.0
	Impulsivity	21 (38)	85.84	44.7
	Standard deviation of response time	26 (38)	87.32	55.3
Executive Function	Category completed	6 (21)	26.19	28.6
	Learning to Learn	11 (21)	18.86	52.4

1. Intelligence (Figure 1, Table 3)

In regards to Intelligence, the group classification by Suzuki stage in left (L) hemisphere showed relatively more group differences. Suzuki stage L1 group performed significantly better in FSIQ and VIQ than Suzuki L4 group. Suzuki stage L1 and L2 groups showed significantly better performance in PIQ compared to Suzuki stage L4 group. Although Suzuki stage L1 group performed better than Suzuki stage L2 group, it did not reach the significant level. In addition, among composite subtests, Suzuki stage L1 group showed a significantly better performance than Suzuki stage L 3 and L4 groups, while groups L1, L2, and L3 scored significantly better in Perceptual Organization than the group L4. Suzuki stage L1 and L2 groups scored significantly better in Attention & Concentration compared to the group L4, while the group L2 scored significantly better in Performance speed than the groups L3 and L4. According to the group classification by Matsushima in the right (R)

hemisphere, they showed significant differences in Perceptual organization and Attention & Concentration amongst FSIQ, PIQ, and composite subtests between subgroups. According to the group classification by Matsushima in the left hemisphere, the group L2 showed a significantly higher IQ than the group L4 and a significant difference between Perceptual Organization and Attention & Concentration just as in Matsushima R group classification. According to the symptom classification, the Moyamoya group with TIA performed significantly better in FSIQ, PIQ and Perceptual Organization IQ than the group with Infarct. Age, sex, and symptom duration did not correlate with the change of neuropsychological results.

Figure 1. Intelligence from Suzuki stage and Matsushima classification.

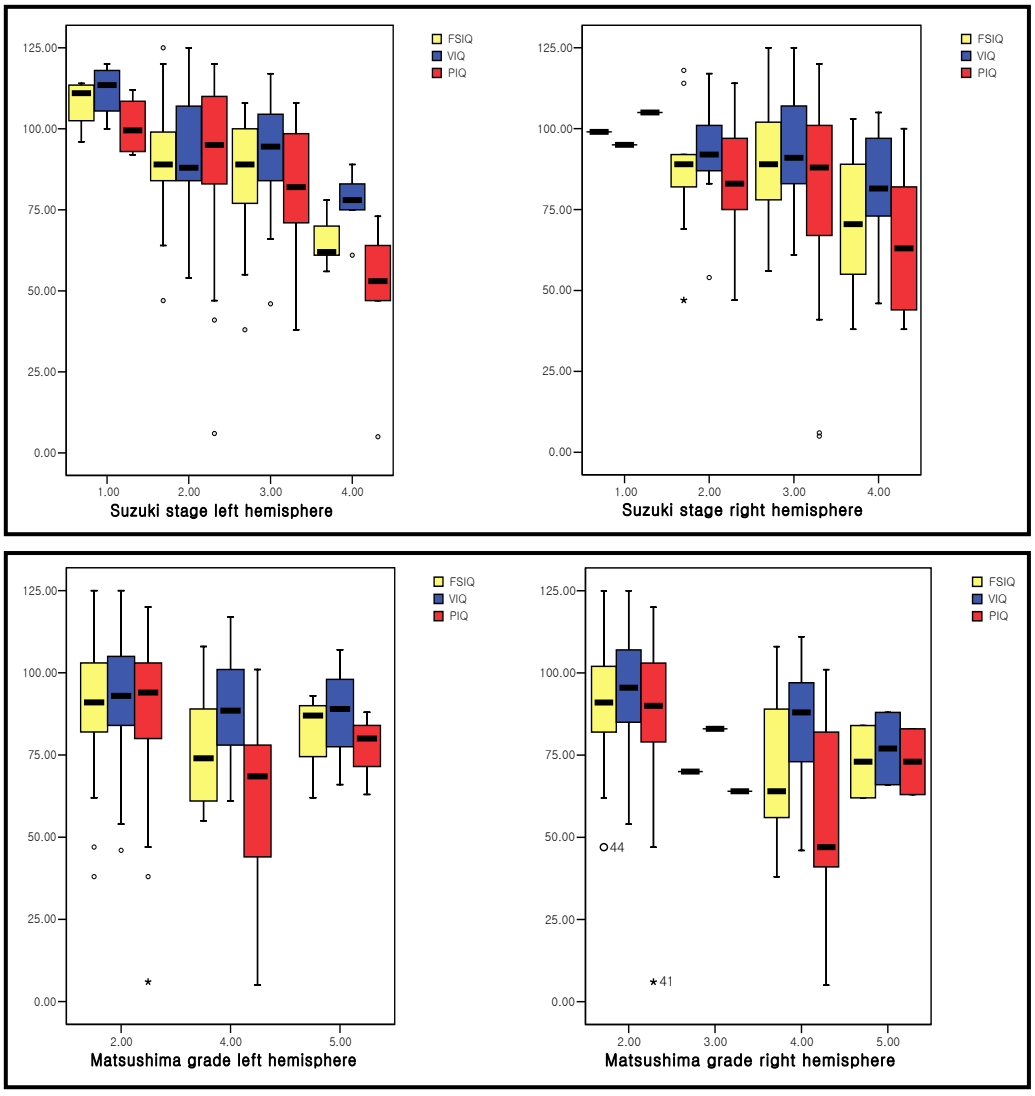

Table 3. Intelligence from Suzuki stage and Matsushima classification.

	Suzuki stage						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 46/46)	1/4	9/13	30/24	6/5	0/0	0/0	
FSIQ	99.0/108.0	87.7/91.2	89.1/85.1	71.0/65.7	0/0	0/0	0.210/0.008
VIQ	95.0/111.8	92.3/92.8	94.2/91.5	80.7/77.2	0/0	0/0	0.410/0.030
PIQ	105.0/100.8	84.9/86.2	81.8/81.2	65.0/48.4	0/0	0/0	0.379/0.013
	Matsushima classification						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 46/46)	0/0	34/33	1/0	9/10	2/3	0/0	
FSIQ	0/0	91.7/90.3	70.0/0	72.4/76.6	86.7/80.7	0/0	0.033/0.143
VIQ	0/0	95.6/93.2	83.0/0	83.1/89.9	77.0/87.3	0/0	0.144/0.782
PIQ	0/0	87.4/87.0	64.0/0	59.0/61.0	73.0/77.0	0/0	0.029/0.022

2. Memory (Table 4)

Thirty one among 46 MMD patients were evaluated memory function. In regards to general memory function, according to the group classification by Suzuki stage R, Suzuki stage R2 group demonstrated significantly higher MQ than Suzuki stage R3, and R4, while the memory quotient of the group R3 was higher than that of group R4 but not to the significant level. Suzuki stage R2 group performed significantly better than Suzuki stage R4 group in immediate recall and delayed recall tasks of Complex Figure Test (CFT) which measures visual memory. Although there were no significant differences in memory quotient amongst the groups according to Matsushima right classification, Matsushima R4 group performed significantly better than Matsushima R2 group in memory retention of Auditory Verbal Learning Test (AVLT) which measures verbal memory.

Table 4. Memory function from Suzuki stage and Matsushima classification.

	Suzuki stage						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 31/31)	0/3	4/7	23/19	4/2	0/0	0/0	
MQ	0/88.7	93.8/98.4	71.8/83.6	67.0/84.0	0/0	0/0	0.012/0.477
	Matsushima classification						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 31/31)	0/0	24/23	1/0	4/5	2/3	0/0	
MQ	0/0	88.5/86.5	113.0/0	73.8/84.0	90.0/100.7	0/0	0.367/0.521

3. Attention (Table 5)

Thirty eight patients were checked attention abilities including inattention, impulsivity, and standard deviation of response time using ADS. The Moyamoya subgroups classified by Suzuki L showed significant group differences in the area of standard deviation of response time. There are no differences in inattention and impulsivity from Suzuki stage and Matsushima classification. In addition, although the Moyamoya group with infarct obtained significantly higher scores than the groups with TIA, it did not show significant differences.

Table 5. Attention from Suzuki stage and Matsushima classification.

	Suzuki stage						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 38/38)	0/3	6/11	26/21	6/3	0/0	0/0	
Inattention	0/54.0	61.7/82.6	80.2/81.4	97.2/86.0	0/0	0/0	0.235/0.574
Impulsivity	0/60.3	87.7/89.4	85.2/88.5	86.8/79.7	0/0	0/0	0.990/0.238
SD	0/69.7	84.3/90.3	86.8/89.8	92.3/78.3	0/0	0/0	0.908/0.008
	Matsushima classification						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 38/38)	0/0	29/29	1/0	7/7	1/2	0/0	
Inattention	0/0	72.9/75.2	58.0/0	111.1/107.3	86.0/52.5	0/0	0.060/0.063
Impulsivity	0/0	76.9/82.8	142.0/0	103.1/108.0	169.0/52.0	0/0	0.809/0.171
SD	0/0	83.1/87.8	68.0/0	96.6/94.7	163.0/55.0	0/0	0.672/0.309

*SD: standard deviation of response time

4. Executive Function (Table 6)

With Executive Function, according to the group classification of Suzuki stage L, Suzuki stage L1 group demonstrated better performances than Suzuki stage L3 group in the rates of total errors and conceptualization and Suzuki stage L2 group than Suzuki stage L3 in Number of 1st trial of WCST. In addition, the symptom classification of groups showed significant differences amongst groups in the rate of total errors and conceptualization.

Table 6. Executive function from Suzuki stage and Matsushima classification.

	Suzuki stage						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 21/21)	0/2	3/7	15/12	3/0	0/0	0/0	
Category competed	0/50.0	33.3/33.2	27.9/18.2	10.7/0	0/0	0/0	0.402/0.089
Learn to learn	0/50.0	87.7/18.7	85.2/13.8	86.8/0	0/0	0/0	0.469/0.115
	Matsushima classification						
	1	2	3	4	5	6	P-value
No (Rt/Lt) (total 21/21)	0/0	16/16	0/0	3/2	2/3	0/0	
Category competed	0/0	30.8/28.6	0/0	14.0/13.0	8.0/22.0	0/0	0.229/0.618
Learn to learn	0/0	24.1/20.7	0/0	3.3/5.0	0.0/18.3	0/0	0.171/0.682

IV. DISCUSSION

Moyamoya disease is a clinical disease entity recognized by its characteristic angiographic pictures and by its unknown pathogenesis. The Japanese Cooperative Study Committee has proposed angiographic criteria for the diagnosis of "definite" cases of this disease as follow: (1) a stenosis or occlusion at the terminal portion of the ICA and at the proximal portions of the ACA and MCA; (2) an abnormal vascular network seen in the arterial phase of the angiograms in the vicinity of the arterial occlusion; (3) indications of bilateral involvement; (4) an absence of any known cause is

also required. No known treatment will reverse the primary disease process, and current treatments are designed to prevent strokes by improving blood flow[2]. Benefit of surgical revascularization for MMD patients is well known. Symptomatic relief and daily living of life in surgical revascularization group is better than non surgical group. A review of literature including fifty-seven studies, which included data from 1,448 patients stated that surgical revascularization had symptomatic benefit about 87% (complete disappearance or reduction in symptomatic cerebral ischemia)[15]. Also, the other literature reported that surgical long term outcome of revascularization surgery in 410 MMD patients was favorable in 81% of the patients[16]. However, in an intellectual point of view, based on several previous reports, natural course of intellectual outcome is poor in pediatric MMD patients. Intellectual problems of a certain group were still continued even though after surgical revascularization[10,17-19]. Matsushima et al. reported the mental prognosis of childhood MMD. Symptom onset of MMD occurs when they are younger than the 5 years old, mental outcomes were very poor even though early operation[10]. Mild intellectual and/or motor impairment was observed in 26% of them and total 24 hours care in 7%. In these studies, early onset of disease, cerebral infarction, or longer disease periods were correlated with poor intellectual outcomes[20]. Intellectual and psychological problem in our study accords with the other literatures. Normal control population showed significantly better scores than MMD patients on intelligence, memory, and executive function. Attention abilities were revealed no differences between two groups. However, most of the research into intellectual outcome of MMD patients has not focused angiographic finding and differences between the right to left hemisphere. The classifications by Suzuki stage and Matsushima with Moyamoya children illustrated consistent differences in Intelligence and Memory ability. Suzuki stage and Matsushima classifications are the classifications according to the degree of progress of MMD. It has been verified that cognitive function declines as the disease progresses. In

particular, the classification by Suzuki stage of left appeared to be most sensitive to the degree of cognitive decline and this seems to suggest that children with left dominance are more sensitive to the decline of left dominance functions. On the other hand, the Matsushima classification showed significant cognitive decline of right dominance functions in the right side rather than the left. Therefore, the result of this study showed that the classification by Suzuki stage is more sensitive to the decline of left dominant functions and the Matsushima classification to the decline of right dominant functions. In terms of symptom classification, the Moyamoya group with TIA maintained significantly better overall cognitive functions than the group with infarct with less attention problems. This seems to be related to the fact that the disease with TIA progresses slower than the one with infarct. And also, according to the progression of angiographic staging especially left sided hemisphere, intelligence and other psychological profiles were generally worsen. Surgical revascularization may improve cognitive function and intelligence as a resulting of improved cerebral perfusion and reducing the risk of TIA and/or cerebral infarction[3,5,21,22]. Ishii et al. reported the effect of surgical revascularization of 15 children with MMD. Postoperatively, most of the patients showed increase in IQ, especially PIQ which improved significantly in ten patients, remained unchanged in three and deteriorated in two[22]. Kuroda et al. assessed significant predictors for poor intellectual outcome in 52 pediatric MMD patients who underwent surgical revascularization[4]. Completed stroke and small craniotomy were independent factors for poor intellectual outcome. However, another literature reported that there were no significant differences between preoperative and postoperative FSIQ and VIQ. PIQ was improved significantly after surgery. So, they asserted that the surgical intervention might prevent the decline of neurocognitive function and early surgical revascularization in MMD patients was recommended to obviate the intellectual decline[23]. Furthermore, Sato et al. reported intellectual outcome

was poor in 69% who underwent surgical revascularization even though reducing or disappearance of ischemic attacks[24]. Based on previous literatures, identifying of MMD as early as possible is essential and early surgical revascularization is mandatory. Several reports have showed that the brain has abilities for adapting to environmental changes. Such neural plasticity, especially in childhood, might be impact in patients with brain injury for certain reasons[25]. So, we think that neuropsychological test must be included on preoperative assessment and early neuropsychological intervention is needed in MMD patients who had intellectual and psychological problems along with early detection of MMD and early surgical procedures.

V. CONCLUSION

Intelligence and other psychological profiles are deteriorated in MMD patients according to the progression of angiographic staging, especially in left dominant function. On the other hand, the progression of disease defined by the Matsushima classification showed significant cognitive decline of right dominant function.

To prevent the decline in intelligence and psychological profiles, we think that the MMD patients who had neuropsychological problems, through the preoperative psychological assessments, may need a neuropsychological intervention.

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ABSTRACT(IN KOREAN)

모야모야 환자에서 Suzuki 단계와 증상 변화에 따른 신경정신학적 변화

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이 윤 호

목적: 모야모야 환자에 있어 반복적인 일과성 허혈증과 대뇌경색에 따른 결과로 소아환자에 있어 진단당시 지적능력 발달에 장애를 가져오는 경우가 있다. 이전 여러 논문에서 소아 모야모야 환자의 지적능력의 문제점들에 대하여 보고한 바 있다. 본 연구의 목적은 Suzuki 단계와 증상 변화에 따라 신경정신학적으로 어떠한 변화를 가져오는가에 대하여 알아 보고자 한다.

연구방법:2008년부터 2009까지 본원에서 모야모야를 확진 받은 46명의 환자에서 수술전 신경정신학적 검사를 실시하였다. 또한, 보원 정신과에서 34명의 정상 아이에 대하여 같은 검사를 실시하였다. 신경정신학적 검사는 지능, 기억력, 주의력, 집행기능에 대하여 검사하였다. 지능은 Korean Wechsler Intelligence Scale for Children-Third Edition (K-WISC-III)로 검사하였으며, 기억력에 대하여는 Rey-Kim Memory Test for Children을 사용하였다. 주의력에 대하여는 Attention-Deficit Hyperactivity Disorder Diagnostic System을 사용하여 검사하였으며, 집행기능에 대하여는 Wisconsin Card Sorting Test를 시행하여 검사하였다. 좌측, 우측의 Suzuki 단계와 증상의 변화 (Matsushima 분류)에 따라 신경정신학적 검사의 변화를 살펴 보았다.

결과: 모야모야 환아의 지능지수(전체 지능지수, 언어성지수, 동작성지수), 기억력, 집행기능에서 정상 아동에 비하여 의미있게 감소하여 있었지만, 부주의와 충동

성지수는 특별한 차이를 보이지 않았다. 좌측 대뇌반구의 Suzuki 단계가 올라감에 따라 전체지능지수, 언어성지능지수, 동작성지능지수가 각각 p-value 0.008, 0.030, 0.013 으로 의미있게 변화하는 것으로 나타났다. 반면에 우측 대뇌반구는 증상 변화에 따라 반복적인 일과성 허혈증상과 뇌경색이 있던 환아에서 전체지능지수 동작성지능지수가 의미있게 감소하는 것을 볼 수 있었다.

결론: 좌측 대뇌반구의 Suzuki 단계에 따라 전체지능지수, 언어성지능지수, 동작성지은지수가 의미있게 변화하는 것으로 나타났으며, 반면에 우측 대뇌반구는 증상 변화에 따라 지능지수의 의미있는 변화를 볼 수 있었다.

핵심되는 말: 모야모야, 신경정신학적 검사, Suzuki단계, 일과성허혈, 뇌경색