COGNITIVE IMPAIRMENT DETECTION IN ADULT THALASSEMIA PATIENT USING MOCA-INA

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ABSTRACT

Background: Cognitive impairment in thalassemia patients are prevalent, therefore early detection of cognitive impairment in adult thalassemia patients is crucial for prevention. Montreal Cognitive Assessment (MoCA) is a public domain cognition screening tools that covers all cognitive domains in detecting mild cognitive impairments.

Objective: To compare cognitive function between adult thalassemia patients and healthy control by using Indonesia version of MoCA test (MoCA-Ina).

Methods: This prospective observational analytic with case control study, compared the total scores and scores of each domain of cognition between adult thalassemia patients and healthy subjects at the Medical Hematology Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia using MoCA-Ina from August to October 2018.

Results: A total of 32 thalassemia subjects and 50 healthy subjects were conducted. A total of 16(50%) subjects in the case group had a value of MoCA-Ina <26, while only 1(2%) healthy control had a value of MoCA-Ina <26. The median total MoCA-Ina score in case and control groups were 25.5 and 27.50 (p <0.001). The median score of memory domains, executive functions and visuospatial of the case and control groups were 3 versus 4 (p <0.001), 3 versus 3.5 (p <0.001) and 3.53 ± 0.671 versus 3.88 ± 0.385 (p <0.003), respectively.

Conclusion: Adults thalassemia patients have lower score in total MoCA-Ina, domains of memory, executive function and visuospatial score compared to healthy control.

Keywords: Cognitive function, MoCA-Ina, thalassemia

Introduction

One of the central neurologic complications in thalassemia patients is cognitive impairment. In most cases, these complications remains sub-clinic symptoms and were only detected in neurological examination and evaluation of neurological imaging.

Hypoxia due to anemia is the main factor that causes cognitive impairment. Iron deposition from an early age, especially in the area of the anterior pituitary gland, cortex, putamen and caudate nucleus results in brain damage that interferes with cognition. Hypercoagulability conditions cause easy occlusion of blood vessels resulting in infarction, in the cortical and subcortical regions, namely the putamen and caudate nucleus. Damage to the cortical and subcortical regions can cause cognitive impairment in thalassemia patients.

Montreal Cognitive Assessment (MoCA) is a global cognition function screening test developed to detect mild cognition disorders, predementia stage. MoCA has advantages as an instrument for detecting cognitive impairments because it covers all cognitive domains including executive function that were not assessed in Mini Mental State Examinations (MMSE) and superiorly in detecting mild cognitive impairment then MMSE and also can be done fast compared to other comprehensive neurocognitive test. MoCA has been validated and has been made the Indonesian version (MoCA-Ina).

Methods

This was a prospective observational analytic case control study with consecutive sampling, conducted in the outpatient clinic of Medical Hematology Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia during August to October 2018. The protocol of the study was approved by the Institutional Ethics Committee. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained prior to participation in the study.

The inclusion criteria were patients above 18 years old, who have already been diagnosed with thalassemia.
undergone regular transfusion in the outpatient clinic of Medical Hematology Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung. Control subjects were healthy population with matching age, gender and educational level, with normal hemoglobin level (Hb) (> 12 g/dL for female and >13g/dL for male) and ferritin serum (22-322 ng/ml for male and 10-291 ng/ml for female). Patients who had hearing disturbances, neurological deficits leading to suspicion of intracranial lesions, history of infectious diseases, head injuries, central nervous system infections, intracranial tumors, epilepsy, chronic health conditions, liver or kidney disturbance based on information collected from medical report, questionnaire and routine neurological examination were excluded from this study.

All eligible subjects were consecutively approached as they came in for their regular transfusion schedule at the outpatient clinic of Medical Hematology Oncology Clinic during data collection period. Written informed consent was obtained prior to participation in the study. At the beginning of the examination and interview, all respondents were informed of the objectives of the study and were assured that all responses would be kept confidential.

All subject undergo cognitive evaluation using MoCA-Ina. The MoCA-Ina value of the case group will be compared with references obtained from the control group in this study. We also obtain data such as education level, hemoglobin level, ferritin level, and body mass index (BMI) in both groups. These variables were known have differences between two groups.

Data analysis was performed using IBM® SPSS® Statistics version 23.0 program. Results were expressed in mean ± standard deviation and median for quantitative variables and in number and percentage for qualitative ones. The MoCA-Ina score between the two groups were compared.

Results

Tabel 1. Demographic data of thalassemia patients and controls

| Variable                  | Thalassemia (n=32) | Controls (n=50) | p-value | Groups                  |
|---------------------------|--------------------|-----------------|---------|-------------------------|
| Sex                       |                    |                 | 0.821   |                         |
| Male                      | 12(37.50%)         | 20(40.00%)      |         |                         |
| Female                    | 20(62.50%)         | 30(60.00%)      |         |                         |
| Age (years)               |                    |                 | 0.456   |                         |
| Median                    | 23,60              | 23,79           |         |                         |
| Range (min-max)           | 18,33-36,76        | 19,20-37,57     |         |                         |
| Education level (years)   |                    |                 | 0.649   |                         |
| Median                    | 12.00              | 10.50           |         |                         |
| Range (min-max)           | 6.00-16.00         | 6.00-16.00      |         |                         |
| Hemoglobin (mg/dl)        |                    |                 | <0.001**|                         |
| Mean±SD                   | 6.98±0.84          | 14.38±1.50      |         |                         |
| Ferritin (ng/dl)          |                    |                 | <0.001**|                         |
| Median                    | 2561               | 46.35           |         |                         |
| Range (min-max)           | 253-11000          | 11-322          |         |                         |
| BMI                       |                    |                 | <0.001**|                         |
| Mean±SD                   | 18.28±2.28         | 22.66±4.089     |         |                         |

Results of MoCA-Ina examination from both groups showed in tabel 2. We obtained a statistically significant difference (p<0,05) in total MoCA-Ina, domains of memory, executive function and visuospatial score between both groups. 16 (50%) subjects in case group has MoCA-Ina score less than 26, while only 1 (2%) subject in control group who has MoCA-Ina score less than 26 (p<0,001***). Case groups has median of total MoCA-Ina 25.50 with details median domains of attention 5.00, language 5.00, memory 3.00, orientation 6.00, visuospatial 4.00, and executive function 3.00. Controlled groups has total MoCA-Ina score 27.50, with details median domains of memory 4.00, orientation 6.00, visuospatial 4.00, language 5.00 while mean of attention were 5.00 and executive function were 3.50.

Tabel 3 showed correlation between hemoglobin, hematocite (Ht), ferritin and Body Mass Index (BMI) to total MoCA-Ina score and each domains (p <0.05). Hemoglobin level and hematocite has positive correlation.
to total MoCA-Ina score (r=0.421 and 0.458), while ferritin has negative correlation (r = -0.314). BMI also has positive correlation (r = 0.352).

The correlation between memory and hemoglobin, hematocite, ferritin and BMI were r=0.368, 0.472, -0.271, 0.342, respectively. Visuospatial has also correlation with hemoglobin, hematocite, ferritin and BMI (r=0.321, 0.291, -0.235 and 0.242). Orientation has positive correlation with BMI (r = 0.253). Executive function has low correlation with hemoglobin, hematocite, ferritin and BMI (r=0.297, 0.323, -0.321, 0.224).

**Discussion**

Most of the subjects were females due to the sampling technique were consecutive sampling. Study by Maatook et al and Trehan et al showed there were no discrepancy in gender of thelessemia patients. Both male and female obtain their gene inheritance by dominant autosomal inheritance.16-18

The median age for this study were 23.60 years old. Elhaniny et al who obtain subjects 18 years and above, showed that the mean age for major thalassemia patients was 25.05±2.61 years old and intermedia thalassemia was 31.15±9.77 years old.19 Life expectancy of thalassemia patients has greatly increased in line with the development of medical science, especially with the usage of iron chelator agents. Iron chelator agents have reduce mortality from 6 times to 2.8 times. Before regular use of iron chelator agents, thalassemia patients who undergo regular blood transfusion died in their teens due to iron deposition in the heart.16,20-23 Study in Iran in 2015 showed the median age of thalassemia patients were 20 years with the range 0.97-56.6 years and the life expectancy thalassemia patients in their 10-, 20-, and 30- years were 98.3%, 88.4% and 80.5%.24

The median levels of education on subjects were 12 years. Study in North America showed that 60% thalassemia patients had education up to college and 14 % had their doctoral degree.25 Study in Cairo in 2016 showed mean education level of major thalassemia and intermedia thalassemia patients were 6.3±3.50 years and 7.90±3.5 years. Various factors influence their education levels, such as the frequency of blood transfusion which makes patients go back and forth to the hospital, obedience to take take the iron chelator medication, self-respect, family support, and their opportunity to go to school. Patients usually have physical complaints as a result from their anemia that leads to disturbance of their performance in school.26,27

Mean BMI of case group were 18.28±2.28kg, which statistically significant compared to control group. There were positive correlation between IMT and total MoCA-Ina score, memory domain, orientation domain, executive function and visuospatial domain. This is due to endocrine dysfunction caused by iron deposition. Endocrine disturbance manifest as disruption of growth hormone (GH) production that leads to interference of growth and development. Hypogonadism, hypothyroid, and disturbance of GH to insulin-like growth factor-1 (IGF-1) as a result of hemosiderosis in pituitary and liver also plays a role in growth disturbance of thalassemia patients.18,28-30

One of the factors which plays a role in ormal growth of major thalassemia children for the first 10 years was their hemoglobin levels. If a child has hemoglobin less that 8.5g/dl, it can leads them to hypoxia condition which becomes main factor of stunted growth. Maintaining hemoglobin levels above 10-11g/dl followed by a proper iron chelator makes major thalassemia patients appears normal dan difficults to distinguish from their peers. Growth delay starting to appears by the age of 10, eventough adequate hemoglobin levels were maintained. Shalitin et all proposed the mean ferritin of 2500ng/ml during puberty was the cut-off point for hipogonadism, and ferritin levels of 3000ng/ml during pre-puberty was the cut-off points of short stature. Gomber and Dewan revealed that if ferritin increased more than 300ng/ml then growth disturbance becomes obvious.29,31

Table 2 showed in general MOCA-Ina score of case group lower compared to control, except for attention, orientation, and language. This result suitable with previous study by Monastero in 2000, which stated that there was cognitive impairment in adult thalassemia patients. Affected domains were attetion, memory, visuospatial and executive function.32 Lestari in 2016 concluded that working memory of major beta thalassemia child patient affects towards their school performance and quality of life.33 Rafaat et all also showed that there was memory disturbance in thalassemia patients.34

Anemia leads disturbance in cognitive by volume changes of basal ganglia and thalamus, associated with lower IQ and memory disturbance.35,36 Lin et all showed that acute isovolemic anemial leads to visuospatial disturbance, working memory and learning disorder, which has been shown in mice model that had hypoxia responce escalation due to anemia.37

High ferritin levels showed iron deposition in body. This iron deposition not only occurred in systemic, but also in brain as hemosiderosis was found in pituitary. Interistingly,
study by Akhlaghpoor et all reveals that thalassemia patients had significantly lower T2* values in basal ganglia (striatum), thalamus and adenohypophysis compared to controls while there were no differences in the midbrain (red nucleus). 38 Study by Lam et all showed that ferritin was found to be associated with T2SI (signal intensity) pituitary and T2 pituitary, and also there was significant correlation of T2SI pituitary with IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). 39

Iron disturbance in adenohypophysis will affect GH and IGF-1. 18,28–30 GH affects the work of limbic and hypothalamus. 30,41 Specific receptors of GH scattered on brain including area related to long-term potentiation (LTP). LTP between two neurons were important components in synaptic plasticity which related with long-term memory (LTM) storage in cellular levels. 42,43 LTP has not detected yet in all parts of brain, but it is clearly found in prefrontal cortex, hypocampus, and amigdala which related to cognitive. 44

Table 3 showed positive correlation between BMI and MoCA-Ina score. Thalassemia patients had lower BMI due to many factors such as growth hormone deficiency, hypothyroidism, hypogonadism, low Hb levels, bone disorders and desferrioxamine toxicity. 45,46

This result corresponds to prior study by Estrella-Castillo et all that all showed subjects with lower weight have poorer cognitive compared to normal population. 47 Study by Joo et all concluded that subjects that have lower BMI has progressive risk to have Alzheimer’s compared to normal 13 while Suemoto et all showed that increase BMI leads to decreased memory function within 12 years. 48

Poor nutritional status can leads to decreased leptin production, lack of vitamin, essential fat and can caused oxidative damage on neuron cells and accelerate degenerative proese of nerve cells. 13,48 Lower leptin serum was found on Alzheimer’s patients with BMI less than 20 compared in patients with BMI > 25. Temporal mesial cortex degeneration which include limbic that plays a role in appetite, eating habit, memory and emotional regulation, all of them can affect weight. 13

Conclusion

Compared to normal subject, thalassemia has cognitive impairment using MoCA-Ina. Hemoglobin and hematocrite has positive correlation to MoCA-Ina score while ferritin has negative correlation.

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