LETTER

Cognitive Examination In Thalassemia Patients

Uni Gamayani1,*, Chandra Calista1, Anam Ong1, Pandji Irani Fianza2 and Ramdan Panigoro3

1Department of Neurology, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, Jalan Pasteur no 38, Bandung, Indonesia
2Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, Jalan Pasteur no 38, Bandung, Indonesia
3Department of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, RSP Unpad, Jalan Eijkman No 38, Bandung, Indonesia

Abstract:

Background:

Many studies on thalassemia patients have shown cognitive decline that may affect the patients’ life. To clarify the cognitive value in thalassemia patients, we performed a neuropsychological test on these patients.

Methods:

This was a prospective observational analytic with case control study involving 40 thalassemia patients and 40 controls similar for age, sex, and education. All subjects underwent a comprehensive neuropsychological test including visual cognitive assessment.

Results:

Compared to controls, patients with thalassemia aged 15-47 years old had poorer results in world list recall (p=0.026), TMT-B (p=0.042), clock drawing test (p=0.049), ADAS-Cog (p=0.014), logical memory (p=0.001) and digit symbol (p<0.001). These results indicate that thalassemia patients have significantly lower attention, verbal memory capability, and executive function.

Conclusion:

Our findings concluded that patients with thalassemia have impaired multiple cognitive domains.

Keywords: Cognitive decline, Neuropsychological test, Thalassemia, Hemoglobin, Multiple cognitive domains, Attention.

1. INTRODUCTION

Thalassemia refers to the inherited defects in the rate of synthesis of one or more of the globin chains of hemoglobin [1]. Thalassemia and hemoglobin (Hb) variant are the most common genetic disorders in Southeast Asia. The prevalence of thalassemia in Indonesia is quite high. Based on the Mean Corpuscular Hemoglobin (MCH), the frequency of α° thalassemia carrier among Javanese, Sumatra and Sulawesi population was 2.6-3.2% and the frequency of -α+ thalassemia carrier in the Javanese, South Sumatra and South Sulawesi population was 2.7%, 10% and 11%, respectively [2].

Thalassemia patients require regular blood transfusions and have to adhere to iron chelation protocols in order to minimize iron overload complications [3]. The life expectancy of thalassemia patients has markedly improved over the last few decades, but patients still suffer from many complications of their congenital chronic disease, and treatment, including neurological complications [4, 5].

Various mechanisms have been studied that lead to neurological complications such as coagulopathy, chronic hypoxia caused by prolonged anemia and iron deposition in the brain [5 - 8].

The introduction of safe transfusion practices, iron chelation therapy, aggressive treatment of infections and improved management of cardiac complications has dramatically improved the life expectancy of thalassemia patients [4, 9 - 11].
The aim of this study was to evaluate cognitive functioning in thalassemia patients with an extensive neuropsychological test

2. METHODS

2.1. Participants and Recruitment

This was a prospective observational analytic with case control study conducted in the Memory Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The thalassemia patients were recruited from outpatient clinic patients of Hematology Oncology Medic Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia between November 2017 until April 2018. The Institutional Ethics Committee approved the protocol of the study.

Inclusion criteria of this study were patients who have already been diagnosed with thalassemia, undergone regular transfusion in the Hematology Oncology Medic Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. While controlled subjects were obtained from healthy individuals with similar age, sex, and education as those of the thalassemia patients.

Patients who had hearing disturbances, history of infectious diseases, chronic health conditions, central nervous system infections, head injuries, intracranial tumors, epilepsy, and other intracranial lesions based on information collected from the medical report, parental report, 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 the Hematology Oncology Medic Clinic during the 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.

2.2. Instruments

Patients and controls were submitted to an extensive standardized neuropsychological test, exploring attention, language, verbal and visual memory, visuospatial and executive function. All subjects were evaluated in our memory clinic. The duration of the test session was approximately 2 hours.

Trail Making Test (TMT) A, vigilance test, digit span and digit symbol were used to evaluate attention. Verbal fluency and Boston naming test were used to evaluate language. Word list memory test, word list recall, word list recognition and logical memory were assessed to evaluate verbal memory while recall constructional was used to evaluate visual memory. TMT B, Clock Drawing Test (CDT), Visual Cognitive Assessment Test (VCAT) were used to evaluate executive function.

2.3. Statistical Analysis

Data analysis was performed using IBM® SPSS® Statistics version 23.0 program. Results were expressed in median for quantitative variables and in number and percentage for qualitative ones. Statistical calculations were conducted in order to compare demographical, clinical and behavioral data between groups. Data were analyzed with Mann Whitney. The possible effect on cognitive functions was assessed with a significance level of p<0.05.

3. RESULTS

The patient group consisted of 17 (42.50%) male and 23 (57.50%) female patients. The median patient age was 20.50 years old. The median years of education were 11 years. There was no statistically significant difference between the two groups regarding age, sex and years of education (Table 1). The p-value for age and education level was assessed with Mann Whitney while gender was assessed with chi-square.

Table 1. Demographic data of thalassemia patients and healthy controls.

| Characteristic          | Thalasemia (n=40) | Control (n=40) | p-value |
|-------------------------|-------------------|---------------|--------|
| Gender                  |                   |               |        |
| Male                    | 17 (42.5%)        | 15 (37.5%)    | 0.648  |
| Female                  | 23 (57.5%)        | 25 (62.5%)    |        |
| Age (years)             |                   |               | 0.070  |
| Median                  | 20.50             | 20.50         |        |
| Range                   | 32 (15-47)        | 34 (14-48)    |        |
| Years of Education      |                   |               | 0.881  |
| Median                  | 11                | 12            |        |
| Range                   | 14 (2-16)         | 10 (6-16)     |        |

From Table 2, the results of VCAT and ADAS-Cog from both groups can be observed. The ADAS-Cog score for the thalassemia group was significantly lower than the control group, while there was no statistically significant difference in the VCAT score.

Table 2. Differences of VCAT and ADAS-Cog between two groups.

| Variables          | Thalasemia (n=40) | Control (n=40) | p-value |
|--------------------|-------------------|---------------|--------|
| Global             |                   |               |        |
| VCAT               |                   |               | 0.084  |
| Median             | 27.50             | 5.00          |        |
| Range (min-max)    | 12 (18-30)        | 3 (2-5)       |        |
| ADAS-Cog           |                   |               | 0.014* |
| Mean               | 6.127±3.286       | 4.452±1.72    |        |
| Median             | 5.30              | 4.3           |        |
| Range (min-max)    | 14 (2-16)         | 7.40 (1.60-9.00) |        |

VCAT = Visual Cognitive Assessment Test, ADAS-Cog= Alzheimer’s Disease Assessment Scale–Cognitive Subscale

From Table 3, it can be seen that the thalassemia group had poor outcomes in the attention, verbal memory and executive function domain compared to the control group. Table 3 shows the p-value of the vigilance and digit symbol as 0.022 and <0.001. The p-value for word list recall and logical memory is shown as 0.026 and 0.001, while p-value of TMT-B and CDT is 0.042 and 0.049.
### Table 3. Neuropsychology test of thalassemia patients and control group.

| Variables      | Thalassemia (n=40) | Control (n=40) | p-value |
|----------------|---------------------|----------------|---------|
| **Attention**  |                     |                |         |
| TMT A          |                     |                | 0.350   |
| Median         | 41                  | 38.50          |         |
| Range (min-max)| 46 (20-66)          | 55 (15-70)     |         |
| **Vigilance**  |                     |                |         |
| Omission       |                     |                | 0.022*  |
| Median         | 00.00               | 0              |         |
| Range (min-max)| 2 (0-2)             | 0              |         |
| Commission     |                     |                | 0.155   |
| Median         | 00.00               | 0              |         |
| Range (min-max)| 1 (0-1)             | 0              |         |
| **Digit Span** |                     |                | 0.370   |
| Median         | 5                   | 5              |         |
| Range (min-max)| 6 (2-8)             | 3 (4-7)        |         |
| **Digit Symbol**|                    |                | <0.001***|
| Median         | 45.50               | 59.50          |         |
| Range (min-max)| 41 (25-66)          | 47 (34-81)     |         |
| **Language**   |                     |                |         |
| Verbal Fluency |                     |                | 0.791   |
| Median         | 20.00               | 21.00          |         |
| Range (min-max)| 19 (13-32)          | 30 (3-33)      |         |
| Boston Naming  |                     |                | 0.961   |
| Median         | 14.00               | 14.00          |         |
| Range (min-max)| 4 (11-15)           | 10 (5-15)      |         |
| **Verbal Memory**|                  |                |         |
| Word List Task |                     |                | 0.367   |
| Median         | 23.00               | 23.50          |         |
| Range (min-max)| 14 (13-27)          | 13 (15-18)     |         |
| Word List Recall|                   |                | 0.026*  |
| Median         | 9.00                | 9.00           |         |
| Range (min-max)| 5 (5-10)            | 6 (4-10)       |         |
| Word List Recognition|    |                | 0.317   |
| Median         | 10.00               | 10.00          |         |
| Range (min-max)| 0 (10)              | 1 (9-10)       |         |
| Logical Memory |                     |                | 0.001***|
| Median         | 9.25                | 12.50          |         |
| Range (min-max)| 13.50 (2.5-16)      | 14.00 (5.50-19.50)| |
| **Visual Memory**|                   |                |         |
| Recall Constructional |    |                | 0.075   |
| Median         | 14.00               | 14.00          |         |
| Range (min-max)| 10 (4-14)           | 7 (7-14)       |         |
| **Visuospatial**|                   |                |         |
| Constitutional Praxis |        |                | 0.105   |
| Median         | 11.00               | 11.00          |         |
| Range (min-max)| 4 (7-11)            | 18 (4-22)      |         |
| Block Design   |                     |                | 0.011   |
| Median         | 4.00                | 4.00           |         |
| Range (min-max)| 4 (0-4)             | 0              |         |
| DTCT           |                     |                | 0.282   |
| Median         | 8.00                | 8.00           |         |
| Range (min-max)| 6 (3-9)             | 2 (7-9)        |         |

**Executive Function**
4. DISCUSSION

Our study showed that thalassemia patients had cognitive impairment compared with the control group. From the various neuropsychological tests that were used in this study, the thalassemia group showed to be statistically lower especially in attention, verbal memory and executive function.

Previous studies regarding cognitive status have been done on thalassemia patients. [12 - 15]. In most studies, thalassemia patients had impaired cognitive function but the impacts on daily life activities were subclinical and usually discovered by comprehensive neuropsychology tests. Monastero et al. conducted the first few studies assessing cognitive functioning in beta-thalassemia patients. From 46 beta-thalassemia major patients and 46 controls, a significantly impaired cognitive function was shown in the former based on all neuropsychological batteries [12].

The study by Ahmadpanah et al. showed that patients with minor beta-thalassemia did not display impaired cognitive performance compared to healthy controls. Hemoglobin levels or gender were also unrelated, but years of education were strongly associated with the level of cognitive performance. From the data, it was shown that individuals with minor beta-thalassemia did not perform poorly on the cognitive test when compared to healthy controls. Even though they did present a causal relationship between the length of education and higher cognitive performance; it is possible that a person with more extended academic achievement has better cognitive knowledge and superior performance than others [16].

Other studies by Zangiabadi et al. and Nevruz et al. reported impairment of cognitive abilities in minor beta-thalassemia patients leading to cognitive deficits [8, 17].

Zangiabadi et al. found lower performances in patients with minor beta-thalassemia in subtests of arithmetic and vocabulary and picture completion. However, both Zangiabadi et al. and Monastero et al. did not evaluate the length of education levels [12, 17].

Attention system is anatomically separate from processing systems, which handle incoming stimuli, make decisions, and produce outputs. Active attention is a multidimensional cognitive process that includes the ability to select and focus on what is important at any given moment, the ability to consistently maintain mental effort while performing tasks that require mental energy and the ability to inhibit action or thought while previewing alternative actions or thoughts. The alerting network is modulated by the brain’s norepinephrine system and involves major nodes in the frontal and parietal cortex. The alert state is critical to high-level performance. The orienting network interacts with sensory systems to improve the priority of information relevant to task performance. The orienting network exerts much of the control over other brain networks during infancy and early childhood. While the executive network is involved in resolving competing actions in tasks where there is conflict. The executive network includes the anterior cingulate cortex, anterior insula, areas of the mid prefrontal cortex, and the underlying striatum [18 - 21].

Memory is a general term for a mental process that allows the individual to store information for later recall. Memory has three stages, which include received and registered, storing or retaining and recall or retrieval. Each stage in the total memory process relies on the integrity of the previous stages. Any interruption in the hierarchy may prevent the storage or retrieval of a memory [22]. Strien et al. explained that each parahippocampal and hippocampal sub-region contributes uniquely to the encoding, consolidation and retrieval of declarative memories [23]. Optitz also explained the role of medial temporal lobe sub-regions, especially of the hippocampus in memory. The hippocampus and the parahippocampal cortex were assumed to support recollection, i.e. recognition of an item on the basis of the retrieval of specific contextual details of the previous learning experience, whereas the perirhinal cortex subserves familiarity, i.e. item recognition on the basis of a scalar memory strength but without retrieval of any specific detail about the study episode [24].

Takeuchi et al. stated that executive functions involve control processes such as goal-oriented planning, flexible strategy generation, sustaining set maintenance, self-monitoring, and inhibition [25]. Executive functions have been associated with functions of the prefrontal cortex in the brain [26 - 28].

The study by Kharat and Waghmare showed that individuals having anemia were more vulnerable to inattentiveness, delayed information analysis, late decision making and slow processing of working memory as compared to the control group [29]. Nemtsas also mentioned that chronic hypoxia and iron overload contribute to neurological manifestations in beta-thalassemia [4].

Iron participates in a wide array of cellular functions and is essential for normal neural development and physiology. But if inappropriately managed, the transition metal is capable of generating neurotoxic reactive oxygen species [30, 31]. In spite of improvements in transfusion practices and the availability of effective iron chelators, the life of thalassemia patients is punctuated by frequent complications. Repeated transfusions and also inadequate chelation can cause patients to have a high level of ferritin serum that leads to iron deposition in the body [32, 33]. But the evidence of iron brain deposition in beta-

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### Table 3 continued...

| Variables | Thalassemia (n=40) | Control (n=40) | p-value |
|-----------|--------------------|---------------|---------|
| TMT B     | 69.50              | 61.50         | 0.042*  |
| Range (min-max) | 112 (30-142) | 91 (25-116)  |         |
| CDT       |                    |               | 0.049*  |
| Range (min-max) | 3.00          | 3.00          |         |

CDT= Clock Drawing Test, DTCT=Drawing To Command Test, TMT= Trail Making Test.
thalassemia patients has never been studied extensively.

Patients with thalassemia have a high prevalence of being in a hypercoagulable state. This is because of the profound hemostatic changes. The presence of a higher than normal incidence of thromboembolic events and the existence of prothrombotic hemostatic anomalies in the majority of the patients have led to the recognition of the existence of a chronic hypercoagulable state in thalassemia patients. Hypercoagulable state in thalassemia can lead to cerebral injury that may interfere with cognitive function in thalassemia patients [34 - 37].

Unfortunately, this study did not assess the depression level between the two groups. In several studies, cognitive symptoms have shown greater impact, because cognition is fundamental to patients’ everyday life. Deficits of cognition may impact psychosocial and workplace engagement. Low mood and cognitive impairment are associated with poor psychosocial functionig [38, 39].

Our study did not assess the Intelligence Quotient (IQ) level of each subject in both groups. Prior assessment of the IQ level may add further information on the cognitive abilities of a person. Subjects can score better if they have IQ up to about 90 or 95 but those cannot improve further whose IQs exceed this range [40 - 42].

The use of iron chelation agents also has an impact on cognition. Deferoxamine (DFO), a clinically used iron chelator, was studied in a mouse model of surgery-induced cognitive dysfunction and its neuroprotective effects on neuroinflammation, oxidative stress, and memory function were assessed. Treatment with an iron chelator, DFO, prevented memory dysfunction in this model by restoring iron homeostasis, neuroinflammation, and oxidative stress [43]. Other chelator agents such as Deferasirox and Deferriprone can also reduce iron burden in transfused patients with thalassemia [44]. Combination of deferisirox and deferoxamine was more effective than deferasirox alone for decreasing iron burden [45].

CONCLUSION

Patients with thalassemia had lower cognitive function especially in domains of attention, verbal memory and executive function compared to the control group. Further research needed to assess intervention could be used to produce better outcomes for thalassemia patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol of the study was approved by the Institutional Ethics Commitee of Universitas Padjadjaran, Indonesia under approval number 66A/UN6.C.10/PN/2017.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. 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.

CONSENT FOR PUBLICATION

Written informed consent was obtained prior to participation in the study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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