ORIGINAL ARTICLE

Assessment of Cognitive Function using the Rowland Universal Dementia Assessment Scale (RUDAS) in Patients with Thalassemia

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Background: Cognitive impairment is frequently found in patients with thalassemia. Advanced age, chronic anemia, iron overload, and hypercoagulability are contributing factors for cognitive dysfunction.

Objective: To determine the prevalence of cognitive impairment and clinical predictive factors in patients with thalassemia.

Materials and Methods: A cross-sectional study was conducted in adult patients aged 18 years or older at Srinagarind Hospital, Khon Kaen University, Thailand, from March to October 2021. The RUDAS test was used to assess cognitive functions. The patients were classified into two groups based on their educational levels; group A (≤6 years of education) and group B (>6 years of education). The RUDAS score <23/30 in group A and <24/30 in group B indicated cognitive impairment. A stepwise backward multiple regression analysis with logarithmic transformations was used to demonstrate the clinical predictive factors for cognitive impairment.

Results: Of 150 patients, cognitive impairment defined by the RUDAS test was found in 28 patients (18.7%). Increased age (adjusted odds ratio [AOR] of 0.9), low activities of daily living (ADL) score (AOR of 0.7), and serum ferritin (AOR of 0.9) were associated with low RUDAS score, which indicated cognitive impairment. Contrary, the interval of blood transfusion (AOR of 1.2) was associated with an increased RUDAS score.

Conclusion: Assessment of cognitive function using the RUDAS test showed a high prevalence of cognitive impairment among thalassemic patients. Aging, low ADL score, and iron overload were significant associated factors with this condition. Cognitive screening should be performed in high-risk patients to modify their risk factors, which may prevent or suspend the progression of cognitive impairment.

Keywords: The RUDAS test; Cognitive impairment; Thalassemia

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Thalassemia is a group of inherited hemoglobinopathies predominantly found in the Mediterranean countries, parts of Africa, China, India, and Southeast Asia including, Thailand[1]. The disease is caused by mutation of the globin genes resulting in decreased production of the globin chains. Imbalanced globin chain is the pathogenesis of the disease leading to ineffective erythropoiesis, which is a pivotal contributing factor for chronic anemia.

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Anemia is well established as a significant factor associated with cognitive dysfunction particularly, in the elderly[2-4]. Individuals with thalassemia were found to have early cognitive impairment compared to the general population. A nationwide population-based retrospective cohort study in patients with thalassemia found that the incidence rates of dementia in women and men with thalassemia were 3.36 and 2.16 per 1,000 person-years[5]. Moreover, the previous studies demonstrated that cognitive impairment in patients with thalassemia is associated with multiple contributing factors including; anemia, reactive oxygen species from iron overload, iron chelation, and hypercoagulable states[6-12].

The Rowland Universal Dementia Assessment Scale (RUDAS) is a 6-item questionnaire. The items are composed of a variety of cognitive domains including, memory, praxis, visuoconstruction, language, and visuospatial domain. It provided a sensitivity of 89% and specificity of 92% at a cutoff point of 23 of 30. Interrater and test-retest reliabilities were 0.99 and 0.98,

respectively[13-15]. The original RUDAS was translated into many languages including, the Thai version. However, RUDAS-Thai revealed less sensitivity and specificity than the English version at the same cutoff point[16]. According to the study by Limpawattana P., et al., they suggest that using the RUDAS-Thai's recommended cut-off points yields similar results to the MMSE-Thai 2002 for dementia screening in geriatric patients. The factor variability in sensitivity and specificity influences educational levels, cultural background, age, language. Thus RUDAS-Thai could be an alternative test to consider in Thai geriatrics as only educational levels affected their test performance[16]. A recent study screened cognitive dysfunction using the RUDAS test in patients with sickle cell anemia. The present study found dementia defined by a low RUDAS score in 29 patients (11.5%), increasing age (r=-0.37; 95% CI, -0.47 to -0.26; p<0.001) and lower glomerular filtration rate (r=0.40; 95% CI, 0.29 to 0.50; p<0.001) were significant associated factors with cognitive impairment[17].

Commonly used cognitive screening tools such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) may not effectively detect cognitive impairment in patients with thalassemia, as their cognitive deficits are not primarily in the memory domain. The RUDAS, on the other hand, measures executive function, which is commonly impaired in these patients, and takes less time to administer than the MoCA[16,18]. Additionally, the RUDAS shows less variation in scores based on educational attainment. Thus, the RUDAS is the preferred tool for assessing cognitive impairment in thalassemia patients in the present study[19].

Thalassemia is a common hemoglobinopathy in Thailand, however, assessment of cognitive function in this population remains limited. In this cross-sectional study, our objective was to demonstrate the prevalence of cognitive impairment and assess clinical risk factors associated with cognitive dysfunction in adult patients with thalassemia.

Materials and Methods

Participants

A cross-sectional study was conducted in adult patients with transfusion-dependent thalassemia (TDT) aged 18 years or older under the project, entitle "Assessment of cognitive function in adult patients with thalassemia" at the Hematology Clinic of Srinagarind Hospital, Khon Kaen, Thailand, from March 2021 to October 2021. Eligible participants were adult thalassemia patients who attended the Hematology Clinic and were enrolled consecutively. We excluded the patients with severe visual, hearing impairment, or motor dysfunction of extremities, patients with known psychiatric problems (included congenital and acquired mental retardation, or a history of psychiatric disease), and patients with an acute medical illness that could impair cognitive performance.

Operational definition and instrument

The RUDAS test

The RUDAS test was completed by a trained physician (TJ) in the Thai language according to the present study by Limpawattana P., et al. The RUDAS scores (Thai version) were evaluated according to the RUDAS-Thai manual for scoring. The patients were divided into two groups based on the educational level including; 1) group A were the patients who had an education level equal or lower than six years, and 2) group B were those patients who had more than six years of education. In group A, any score lower than 23/30 indicated major cognitive impairment (dementia). For group B, any score lower than 24/30 suggested major cognitive impairment (dementia). Scores higher than the cut point depending on their educational level were normal. The RUDAS score (Thai version) provided a sensitivity of 89% and specificity of 92% at a cutoff point of 23 of 30.

Procedure

All eligible participants were invited to participate in the research project. After obtaining the informed consent, the participants were assessed for the RUDAS score by a physician (TJ). Medical histories that the literature indicated as risk factors for cognitive impairment were collected as follows; gender, age, educational level, occupation, alcohol and smoking status, thalassemia genotype, history of blood transfusion, iron chelation therapy, and comorbidities. Laboratory parameters that are potential risk factors were evaluated (e.g., hemoglobin (Hb), serum ferritin, and blood chemistry). All participants were also evaluated for the Patient health questionnaire-9 (PHQ-9) and activity daily life (ADL) score. PHQ-9 scores were used to screen depression, any score greater than 8 points was suggestive of depression. ADL score represents the daily ability status the score >20 indicated impaired ADLs).

Ethical approval was provided by the ethics committee of the Faculty of Medicine, Khon Kaen University under the respect of the Helsinki Declaration (HE641068).

Statistical analysis

All statistical analysis was performed by the STATA version10.0 (StataCorp, College Station, Texas). Continuous variables were presented as median and interquartile range (IQR). Categorical variables were reported as number and percentage. Univariate analysis and stepwise backward multiple regression with logarithmic transformations was used to determine the correlation of the RUDAS scores and the associated factors. Adjusted odd ratio (AOR) and their 95% confidence intervals (CI) were

reported to denote the strength of association. A p-values less than 0.05 were considered as having statistical significance.

Results

One hundred and sixty eligible patients were screening in this study, 10 patients were excluded (8 patients with auditory problems and 2 patients with acute medical illness). Therefore, the remaining 150 patients were recruited in this cohort. Of 150 patients, cognitive impairment defined by the RUDAS score based on education level was found in 28 patients (18.7%) in this cohort. Waterfall plot of the RUDAS scores in group A and group B were shown in Figure 1. Among 30 patients in group A (≤6 years of education), cognitive impairment defined by the scores lower than 23 was found in 7 patients (23.3%). For group B (>6 years of education), cognitive impairment defined by the scores lower than 24 was found in 21 patients from 120 patients (17.5%).

Table 1 demonstrates the patients' baseline data. The median age was 33 (IQR=24, 48). All of these, 82 were male (54.7%). The median RUDAS scores was 29 (IQR=25, 30). The majority of participants in this cohort had education levels of more than six years (120, 80%). HbE/beta-thalassemia was the most common genotype of thalassemia (113, 75.3%) in the present study. The median interval between blood transfusions was 6 weeks (IQR=4, 8). Almost all patients (137, 91.3%) had current iron chelation treatment. Cholelithiasis was the most common thalassemia-related complication (41, 27.3%) followed by extramedullary hematopoiesis (23, 15.3%), and hypothyroidism (17, 11.3%). Hypertension was the most comorbidity disease (18, 12%) followed by chronic kidney disease (14, 9.3%).

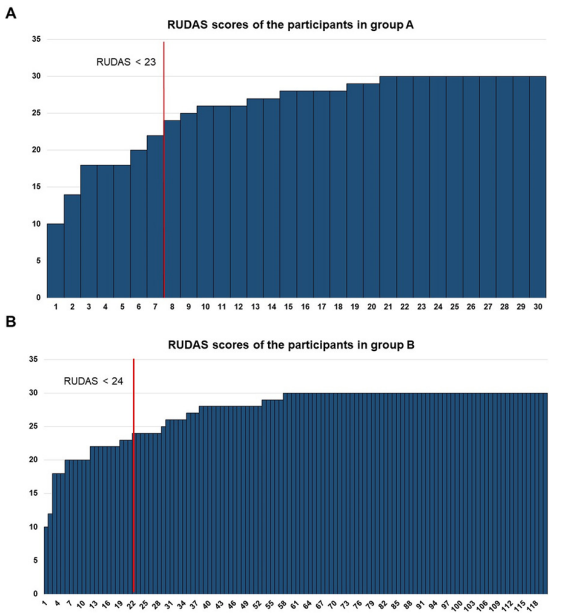

Figure 1. Waterfall plot of the RUDAS scores in group A and group B.
A) Waterfall plot of the RUDAS scores in group A (≤6 years of education); B) Waterfall plot of the RUDAS scores in group B (>6 years of education)

Factors associated with cognitive impairment using the RUDAS scores

According to stepwise backward multiple regression analysis with logarithmic transformations, advanced age (AOR of 0.9, 95% CI 0.8 to 0.9, p-value <0.05), low ADL score (AOR of 0.7, 95% CI 0.6 to 0.9, p-value <0.05), and increased serum ferritin levels (AOR of 0.9, 95% CI 0.8 to 0.9, p-value <0.05) were statistically significant with cognitive impairment. The increasing interval between blood transfusions was associated with increased RUDAS scores (AOR of 1.2, 95% CI 1.01 to 1.6, p-value=0.019), which is negatively correlated with cognitive impairment in the present study (Table 2).

Discussion

Cognitive impairment defined by the RUDAS scoring based on their educational level was high (28/150, 18.7%) in the present study. These results consistent with the literature showed high cognitive dysfunction in patients with thalassemia compared to the general population. Aging, low ADL score, and iron overload were principal risk factors associated with cognitive impairment in this cohort.

Secondary hemochromatosis was common among patients with thalassemia. Chronic blood transfusion and increased intestinal iron absorption are leading causes of iron overload in these populations. Iron is an essential element for normal brain development and cognitive function. Therefore, both iron deficiency and iron overload impact neurological development and function. Accumulation of iron in the brain increases progressively with age, particularly in the cortex and the nuclei of the basal ganglia, putamen, globus pallidus, and caudate nucleus. An accumulation of iron in these regions is associated with many neurodegenerative disorders, some psychiatric disorders, and cognitive impairment. Therefore, iron overload in patients with thalassemia is one of the principal factors that impair cognitive functions. The present study found that serum ferritin was significantly associated with decreased RUDAS scores (AOR of 0.9, p-value <0.05), which indicated cognitive impairment. These findings comparable to the previous studies in thalassemia patients found that iron overload is a significant risk factor for cognitive dysfunctions. The negative effects of enhanced iron in the brain have been proposed to an oxidative damage component, iron-mediated regulated cell death pathway, and ferroptosis. It is now mentioned its role in neurodegenerative

Table 1. Baseline data of the participants

Variables	All participants (n=150)	Normal RUDAS score (n=122)	Low RUDAS score (n=28)
Age (years), med (IQR)	33 (24, 48)	30 (22, 40)	54 (36, 68)
Gender			
Male, n (%)	82 (54.7)	69 (56.5)	13 (46.4)
Female, n (%)	68 (45.3)	53 (43.5)	15 (53.6)
Educational level; n (%)			
<6 years education	30 (20)	23 (18.9)	7 (25)
>6 years education	120 (80)	99 (81.1)	21 (75)
Types of thalassemia; n (%)			
Beta-thalassemia	113 (75.3)	93 (76.2)	20 (71.4)
Alpha-thalassemia	37 (24.7)	29 (23.8))	8 (28.6)
Interval between blood transfusions (weeks), med (IQR)	6 (4, 8)	6 (4, 8)	4 (2, 6)
Iron chelation treatment, n (%)	137 (91.3)	115(94.2)	22 (18.5)
Thalassemia-related complications; n (%)			
Pulmonary hypertension	19 (12.7)	11 (9.0)	8 (28.6)
Heart failure	13 (8.7)	7 (5.7)	6 (21.4)
Extramedullary hematopoiesis	23 (15.3)	18 (14.7)	5 (17.8)
Fracture	8 (5.3)	5 (4.1)	3 (10.7)
Cholelithiasis	41 (27.3)	32 (26.2)	9 (32.4)
Diabetes mellitus	15 (10)	12 (9.8)	3 (10.7)
Hypothyroidism	17 (11.3)	13 (10.6)	4 (14.3)
Hypogonadism	4 (2.7)	3 (2.4)	1 (3.5)
Thrombosis	8 (5.3)	5 (4.1)	3 (10.7)
Co-morbid disease(s); n (%)			
Hypertension	18 (12)	9 (7.3)	9 (32.1)
Obesity	5 (3.3)	4 (3.2)	1 (3.5)
Chronic kidney disease	14 (9.3)	5 (4.1)	9 (32.1)
Dyslipidemia	6 (4)	1 (0.8)	5 (17.8)
Stroke	4 (2.7)	2 (1.6)	2 (7.1)
Current smoking; n (%)	13 (8.7)	10 (8.2)	3 (10.7)
Regular alcohol drinking unit	5 (3.3)	5 (4.1)	0 (0)
Hemoglobin (g/dL); med, IQR	7.9 (7.0, 8.8)	7.8 (6.9, 8.7)	8.1 (7.2, 8.8)
Ferritin (ng/mL)	1,393 (790, 2,592)	1,212 (714, 2,183)	2,128 (1,536, 3,379)
PHQ9 scores; med, IQR	2 (0, 5)	2 (0, 4)	4.5 (2, 8)
ADL scores; med, IQR	16 (16, 16)	16 (16, 16)	16 (16, 24.5)
RUDAS scores; med, IQR	29 (25, 30)	30 (28, 30)	20 (18, 22)

IQR=interquartile range; PHQ-9=Patient health questionnaire-9; ADL=activity daily life; RUDAS=The Rowland Universal Dementia Assessment Scale

diseases and cognitive impairment. Furthermore, systemic inflammation can be increased during blood transfusion and has also been reported to be involved in the pathogenesis of neurodegeneration and cognitive impairment[9,20-22].

Advanced age is well known as a significant risk factor of cognitive impairments in the general population[23]. The development of these conditions is a time-dependent process, therefore, increasing age results in an increased risk of development of cognitive dysfunctions. In the present study, aging was a crucial factor associated with low RUDAS scores (AOR of 0.9, p-value <0.05) suggesting cognitive impairment in patients with thalassemia.

Activities of daily life (ADL) are essential and routine tasks that most young, healthy individuals can perform without assistance. The inability to accomplish essential ADL may lead to unsafe conditions and poor quality of life[24]. Thus, the inability to live dependent, mentioned as a low ADL score, may indicate cognitive impairment. Our study showed that low ADL score (AOR of 0.7, p-value <0.05) associated with low RUDAS score.

Anemia is one of the main risk factors for cognitive impairments. In this cohort, the increasing interval of blood

Table 2. Factors associated with RUDAS scores using multiple regression analysis with logarithmic transformations

Variables	AOR	95% CI	p-value
Age	0.9	0.8 to 0.9	<0.05
ADL scores	0.7	0.6 to 0.9	<0.05
Iron chelation therapy	4.8	0.5 to 44.4	0.167
Interval of blood transfusion (week)	1.2	1.01 to 1.6	0.019
Diabetes mellitus	5.3	0.7 to 37.6	0.094
Chronic kidney disease	0.1	0.0 to 1.9	0.133
Obesity	0.1	0.0 to 3.4	0.229
Dyslipidemia	21.0	0.6 to 677.7	0.085
Pulmonary hypertension	3.4	0.5 to 22.3	0.197
Serum ferritin (ng/mL)	0.9	0.8 to 0.9	<0.05
PHQ-9	0.8	0.7 to 1.0	0.068

AOR=adjusted odds ratio; 95% CI=95% confidence interval

transfusion was associated with increased RUDAS scores (AOR of 1.2, p-value=0.019). This finding might be due to patients who had a long interval of blood transfusion having higher pre-transfused hemoglobin than those who had a short interval of blood transfusion. In the present study, stroke, diabetes mellitus, chronic kidney disease, dyslipidemia, and depression were not statistically associated with cognitive impairment, which may be due to the limited number of events.

Previous studies have also evaluated cognitive impairment in patients with thalassemia using methods such as brain magnetic resonance imaging (MRI) for evaluating parenchymal, vascular, and iron content, as well as biomarkers[8,22]. However, there is currently no standard guideline for assessing cognitive function in patients with thalassemia. Our study revealed a high prevalence of cognitive impairment in adult patients with thalassemia. Based on our results, the authors suggest that early screening or diagnosis of cognitive dysfunction should be incorporated into the routine standard care for thalassemic patients to improve their quality of life and benefit society.

The present study had some limitations. First, there is no standard cut-off point of the RUDAS score suggestive of cognitive impairment in younger adults (age <65 years). Second, the RUDAS test had not been validated in this particular population. However, it is practical and can be used as a screening tool for the early detection of cognitive dysfunction.

Conclusion

Cognitive impairment defined by the RUDAS test is high among patients with thalassemia. Aging, low ADL score, and iron overload were pivotal risk factors associated with cognitive dysfunction. Early screening should be performed in high-risk patients to improve iron chelation therapy, blood transfusion, and effective leisure activity life promotion, which may suspend the progression of this condition in patients with thalassemia.

What is already known on this topic?

Cognitive impairment is frequently found in patients with thalassemia. Chronic anemia, aging, iron overload, and hypercoagulability are well known clinical risk factors for cognitive dysfunction in these patients. However, assessment of cognitive function in Thai patients with thalassemia remains limited.

What this study adds?

The present study demonstrated a high prevalence of cognitive impairment defined by the RUDAS test among Thai patients with thalassemia. Aging, low ADL score, and iron overload were significant risk factors associated with cognitive dysfunction in these patients.

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Conflicts of interest

The authors declare no conflict of interest.

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