Clinical Silent Cerebral Infarct (SCI) in Patients with Thalassemia Diseases Assessed by Magnetic Resonance Imaging (MRI)

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Background: *Silent cerebral infarct (SCI) could be detected on magnetic resonance imaging. It seems to be associated with the risk of stroke. Ischemic stroke has been reported in sickle cell anemia. Sickle red cell in hypoxic state associated with hypercoagulopathy is the risk factor of blood vessel occlusion leading to ischemic stroke. Hypercoagulable state has been documented in patients with β thalassemia/Hb E disease, which their red cells are abnormal in deformity.*
Objective: *Explore SCI in patients with β thalassemia/Hb E disease and provide a guideline for prevention of stroke.*
Material and Method: *Sixty-seven patients (29 males and 28 females, age 10-59 yrs, with a mean age of 31) with β-thal/Hb E disease who were in the steady state without any neurological sign and symptom and no other associated stroke related disease such as DM, HT were included for MRI.scanning. The cerebral MRI protocals were axial Flair, T2 Gre and 3DTOFMRA (3-dimension time of flight magnetic resonance angiography) of the brain.*
Results: *67 patients (29 males and 28 females) with β-thal/Hb E disease who were in the steady state without any neurological sign and symptom and no other associate stroke related disease such as DM, HT were included for MRI scanning. The ages of the patients were 10 to 59 years with a mean of 31 years. The abnormalities of the brain were found in 16 of 67 (24%). Most of the lesions were lacunar infarcts with varying amounts in the deep cerebral white matter. One cortical and subcortical infarct was observed with irregularity and stenosis of the intracranial vessels noted by MRA. All cases showed increased vascularity compared to the normal control subject.*
Conclusion: *This preliminary prevalence of 24% of SCI in this genotype of thalassemia was higher than found in sickle cell disease (11%). It may be associated with coagulopathy and deformity of the red cell. Further study is needed.*

Keywords: *Cerebral infarction, Thallassaemia, Magnetic resonance imaging*

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Cerebrovascular disease (CVD) is the first leading cause of morbidity and mortality of Thai females and the first leading cause of morbidity as well as third leading cause of mortality of Thai males[1]. A recent report suggests a prevalence of clinical CVD in the elderly patient (older than 65 yrs) of about 5% and 1.5% for stroke and transient ischemic attack, respectively[2]. Furthermore, the prevalence of stroke in the elderly Thai people is 1.12%[3], which is rather different between the two races. There is even less information on the prevalence of silent cerebral infarct (SCI). With the advent of magnetic resonance imaging (MRI), it has been possible to evaluate SCI in majority of the subclinical case of CVD. In patients with sickle-cell

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disease, the prevalence of SCI has been reported in about 11%[4-6]. SCI could be seen on MRI in elderly healthy persons. It seems to be associated with the risk of stroke. There is no clear cut of the risk factors between SCI and symptomatic stroke. Ischemic stroke has been reported in sickle cell anemia. Sickle red cell in hypoxic state associated with hyper-coagulopathy is the risk factor of blood vessel occlusion leading to ischemic stroke. Hyper-coagulable state has been documented in patients with β thalassemia/Hb E disease in which their red cells are abnormal in deformity. This study will explore SCI in these patients and will become a guideline for prevention of stroke.

Material and Method

Sixty-seven patients (29 males and 38 females) with β-thal/Hb E disease who are in the steady state without any neurological sign and symptom were included for MRI scanning. The cerebral MRI protocals were axial Flair, T2 Gre and 3DTOFMRA (3-dimension time of flight magnetic resonance angiography) of the brain.

The images were displayed on the workstation monitors for evaluation by an experienced neuroradiologist. SCIs were defined as focal, non-mass lesions having arterial vascular distribution and being hyperintense on T2 or Flair sequences. Lacunar SCI was documented when the lesion was smaller than 10 mms in diameter. The dimensions of the lesions were measured using electronic curser.

For anatomic localization, lesions were assigned to one or more 12 regions: ACA, MCA, PCA, mid brain, pon, superior cerebellar, AICA, PICA, cortical, subcortical, deep WM, or neuclei.

For statistic analysis, mean ± standard deviation (SD) for continuous variable and percentage for counting number were summarized and t-test was used to determine statistical relationship of age, gender, and SCIs. A p-value of ≤ 0.05 was considered statistically significant.

Results

Sixty-seven patients with β-thal/Hb E disease were included in the present study, 29 males, and 38 females. Age of the patients was 10 to 59 years with mean of 31 years. The abnormalities of the brain were found in 16 of 67 (24%). Most of the lesions were lacunar SCI (Fig. 1) with varying amounts in the deep cerebral white matters. Cortical and subcortical infarct was also observed. The data is presented in Table 1, 2, and 3. The irregularity and stenosis of the intracranial vessels is noted by MRA in one case with cortical SCI as shown in Fig. 2 and 3. Overall, all cases revealed increased vascularity. No difference between the levels of Hb/Hct as correlated to the present of SCI as well

Table 1. SCI with age gender

	Number of SCI	Study population	% of SCI/ study population	p-value
Age				
1-20	1	14	7	
21-40	10	41	24	
41-60	5	12	42	
Total	16	67	23	.05
Gender				
Male	9	29	31	
Female	7	38	18	
Total	16	67	24	.05

Note: p-value and % are adjusted for age and gender

Table 2. Anatomic localization of the SCI and size

Lesion location.	No. of cases	No. of SCI	Size
ACA	2	3	
MCA	14	40	
PCA	0		
Supratentriuml subtotal	16	43	
Mid brain	0		
Pon	0		
Superior cerebellar	0		
AICA	0		
PICA	0		
infratentorium subtotal	0	0	
Total	16	43	
Cortical & subcortical	1	2	> 10 mms
Deep WM and neuclei	15	41	≤ 10 mms
Total	16	43	

ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, AICA = anterior inferior cerebellar artery, PICA = posterior inferiorcerebellar artery

Table 3. SCI vs. Hb, Hct and splenectomy

	Positive SCI	Negative SCI
Hb/Hct	10.7 ± 1.6/32.4 ± 2.9	10.9 ± 1.2/31.5 ± 3.2
Splenectomy	1/16	3/51

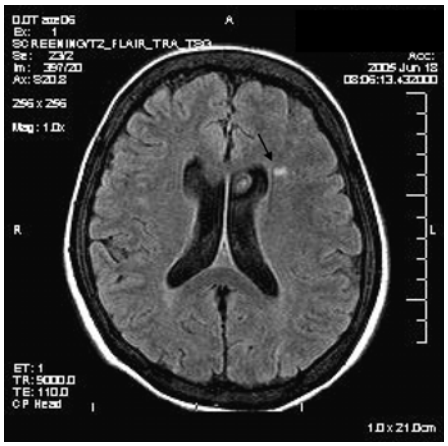


Fig. 1 Lacunar SCI (arrow) at left centrum semi ovale

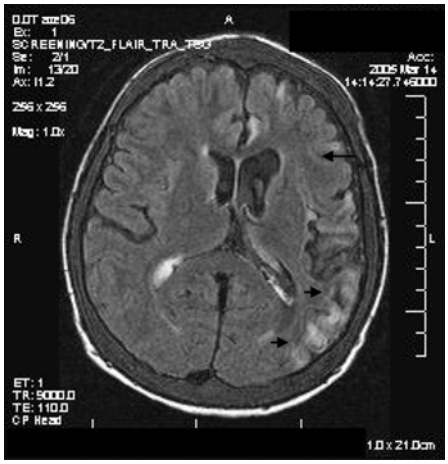


Fig. 2 Cortical and subcortical SCI (arrows) at left fronto-temporal lobe

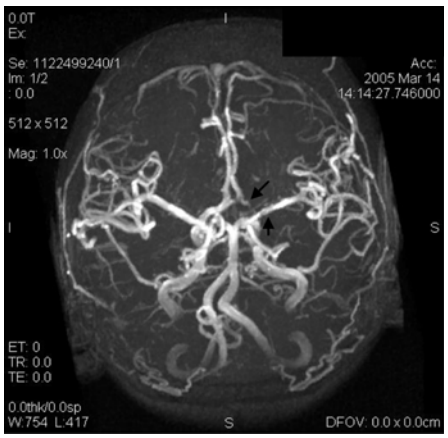
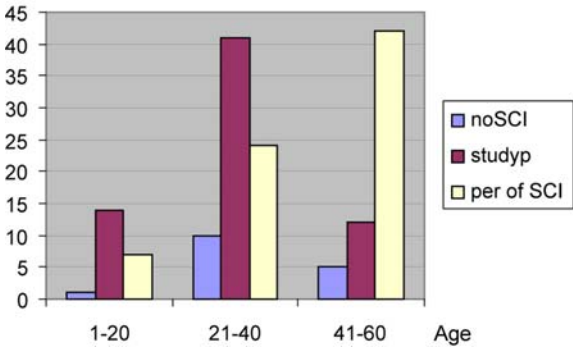
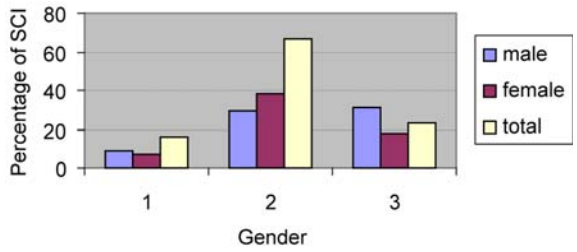


Fig. 3 Irregularity and stenosis of left A1 and M1 (arrows), same patient in Fig. 2 with marked increased vascularity



noSCI = number of SCI
studyp = study pupulation
per of SCI = percent of SCI/popuation

Graph 1. Percentage of SCI vs. age



1 = number of SCI, 2 = number of study population,
3 = percentage of SCI/study population

Graph 2. Percentage of SCI vs. gender

as the splenectomy (Table 3). More prevalence of SCI in males rather than females, 31% vs. 18% (Graph 2) was noticed and the prevalence seemed to be increasing with age (Graph 1).

Discussion

MRI has revealed SCI of the brain in a large percentage of adults, especially the elderly, although the nature and significance of these lesions were still unknown. However, it has become increasingly clear that they reflect small-vessel ischemic disease of the brain[7-13]. The actual prevalence of this condition has been documented by some studies. The CHS reported a prevalence SCI of 36%, a six-time greater than prevalence of clinical stroke/TIA in that elderly population[8]. The prevalence of SCI in a younger population has been poorly documented and even never reported in the thalassemia patient, leading to the main focus of this report.

Although there are many descriptive papers reporting putative CT and MR findings of CVD, including infarct, white matters SI (signal intensity) change,and cerebral atrophy[4,9-11], it should be noted that much of this literatures focused on T2 hyper SI. Lindgren et al recently reported the prevalence of asymptomatic abnormalities on MRI in a Swedish population-based study of 77 participants who were 36-95 years old and some of these participants resembling the presented SCI[14].

One of the most extensive population studies of the prevalence of CVD, clinical and subclinical is CHS[2,8]. The study was similar in design to the present study except for its older population and not thalassemia. The overall prevalence of SCI on the MRI of the CHS participants was 36% vs. 24% in the present study[8]. In both studies, SCI increased with age.In the CHS study, the oldest group, ranging from 85-97 years old, had SCI prevalence of 43% rather equal to 42% of SCI in the present study (age ranging 41-60), which is much younger. This finding suggests the more risk of SCI in thalassemic patients.

As in the CHS, approximately 72% of SCI in the present study were less than 10 mms in diameter and were in the deep WM and neuclei, consistent with lacunar infarct. In both CHS and the present study, males had a significantly higher prevalence of SCI than females and showed similar anatomic characteristics of SCI, suggesting the common patholphysilogic substrate.

Although the cause of SCI is uncertain, based on MRI and previously demonstrated associations between SCI and stroke/TIA symptoms as well as other neurological abnormalities, a vascular cause seem most likely[6,15]. The appearance of the larger cortical lesion is consistent with generally accepted description of cerebral infarct[12,16,17]. Although the nature of smaller lesions especially those in the deep neuclei, may be controversial, the authors think that they are ischemic in origin and compatible with lacunar infarct, these lesions are bright in T2W images[15,21]. Furthermore, the lesions are most common in the deep WM zones where small penetrating arteries terminate in vascular territories[9]. These lesions are small; most lesions are less than 10 mms in maximal diameter. Multiple lesions are frequent and they are associated with increased age.

The prevalence of SCI in sickle cell disease has been reported to be 11%[4-6]. This disease is similar to thalassemia disease in the present study. Both diseases have deformed red cell. The prevalence of SCI of thalasseamia in the present study is 24%, about two-times of the sickle cell disease. Sickle red cell in hypoxic state associated with hypercoagulopathy leading to small blood vessel occlusion. Hypercoagulable state has been documented in patients with β-thalassemia in which their red cells are abnormal in deformity. This suggests that the deformity of the red cell in thalassemia may be leading to more prevalence of SCI. It would be interesting to explore SCI in these patients to create a guideline for prevention of stroke in these patients. In the present study, the increased vascularity in all cases may be the compensating mechanism to the anemic status as well as the hypertrophy of bone marrow and extramedullary hemotopoiesis. This preliminary prevalence of 24% of SCI in this genotype of thalassemia is higher than was found in sickle cell disease (11%). It may be associated with coagulopathy and deformity of the red cell. Further studies are needed.

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การศึกษาภาพ เอ็ม อาร์ ไอ ของสมองในผู้ป่วยธาลัสซีเมีย เพื่อดูความชุกของรอยโรคสมองขาดเลือดที่ไม่มีอาการ

พิเชษฐ เมธารักษ์ชีพ, สมศักดิ์ จรรยาวัติวงศ์, กมลรัตน์ ศรีสุบัติ, เพ็ญศรี ภู่ตระกูล

วัตถุประสงค์: *รอยโรคของสมองขาดเลือดที่ไม่มีอาการสามารถเห็นได้บ่อยในคนสูงอายุ และดูเหมือนว่าจะเกี่ยวข้องกับความเสี่ยงในการเกิดโรคสมองขาดเลือด เคยมีรายงานโรคสมองขาดเลือดในผู้ป่วยโรคซิคเคิลเซลล์ ซึ่งในภาวะที่ขาดออกซิเจนเลือดจะข้นและเหนียว ทำให้เสี่ยงต่อการอุดตันของหลอดเลือด ภาวะเลือดข้นและเหนียวได้ เคยมีรายงานในผู้ป่วยโรคธาลัสซีเมีย ซึ่งมีความผิดปกติของเม็ดเลือดแดง จึงเป็นที่น่าสนใจอย่างยิ่งที่จะศึกษาในผู้ป่วยเหล่านี้ และบางทีผลการศึกษาอาจใช้เป็นแนวทางในการป้องกันไม่ให้เกิดโรคสมองขาดเลือด*

วัสดุและวิธีการ: *ผู้ป่วยจำนวน 67 รายที่เป็นโรคธาลัสซีเมีย และไม่มีอาการของสมองขาดเลือด ได้รับการทำ เอ็ม อาร์ ไอ เพื่อดูรอยโรคสมองขาดเลือด รวมทั้งตรวจดูหลอดเลือดที่ไปเลี้ยงสมอง ผู้ป่วยที่ศึกษามีอายุอยู่ระหว่าง 10 ถึง 59 ปี อายุเฉลี่ย 31 ปี เพศชาย 29 คน เพศหญิง 38 คน*

ผลการศึกษา: *พบรอยโรคสมองขาดเลือด 16 ราย จาก 67 ราย เท่ากับร้อยละ 24 ส่วนใหญ่เป็นรอยโรคขนาดเล็กที่บริเวณส่วนลึกของสมอง มี 1 ราย ที่พบบริเวณผิวสมอง ซึ่งในรายนี้มีหลอดเลือดสมองตีบร่วมด้วย และทุกรายพบว่ามีการเพิ่มขึ้นของหลอดเลือดที่ไปเลี้ยงสมอง*

สรุป: *รายงานเบื้องต้นเกี่ยวกับความชุกของรอยโรคสมองขาดเลือด ที่ไม่มีอาการในผู้ป่วยโรคธาลัสซีเมีย เท่ากับร้อยละ 24 ซึ่งมากกว่าผู้ป่วยโรคซิคเคิลเซลล์ที่พบเพียงร้อยละ 11 และดูจะเกี่ยวข้องกับภาวะข้นเหนียวของเลือดและความผิดปกติของเม็ดเลือดแดง จึงจำเป็นอย่างยิ่งที่จะต้องศึกษาอย่างละเอียดต่อไป*