pISSN 2302-1381
eISSN 2338-4506

IJIHS International Journal of Integrated Health Sciences

Original Articles

Case Reports

Volume 9, Number 1, March, 2021

Erythropoiesis Differences in Various Clinical Phases of Dengue Fever using Immature Reticulocyte Fraction Parameter

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.1805
IJIHS. 2021;9(1):7–12

Received:
October 18, 2020

Accepted:
March 30, 2021

Abstract

Objective: To determine the mechanism of erythropoiesis that led to anemia using the Immature Reticulocyte Fraction (IRF) parameter in various clinical phases of dengue fever.

Methods: This study was a comparative analytical research using secondary data derived from the *Dengue-associated Endothelial Cell Dysfunction and Thrombocyte Activation* (DECENT) research. The study was performed at Dr. Hasan Sadikin Hospital Bandung, Indonesia from March 2011 to March 2012. Patients were grouped into fever, critical, recovery, and convalescent phases and a healthy control was established. Data collected were analyzed using the Kolmogorov-Smirnov normality test, followed by Friedman test and Mann-Whitney post hoc test.

Results: There were 244 subjects participating in this study. The median IRF for all subjects was 4.8% with an IQR of 2.4-8.1%. The values of Immature Reticulocyte Fraction in fever-phase, critical-phase, recovery-phase, convalescent-phase and healthy-control were 1.8% (IQR of 0.5–2.85%), 3.6% (IQR of 1.8–5.0%), 7.05% (IQR of 4.08–11.85%, 7.3% (IQR of 3.95–9.3%) and 4.1% (IQR of 2.2-6.6%), respectively. There was a significant difference in IRF between groups ($p<0.05$). The immature Reticulocyte Fraction in fever phase was significantly different from the IRF in other phases and healthy controls ($p<0.05$).

Conclusions: There are changes in erythropoiesis activities detected through the IRF in various clinical phases of dengue infection. Erythropoiesis suppression occurs mainly during the fever phase and starts to be restored in the critical phase. In the recovery and convalescent phases, the erythropoiesis activities increase. This is the first study describing IRF in multiple phases of dengue disease.

Keywords: Diastolic dysfunction, hypertensive heart disease, left ventricular hypertrophy, matrix metalloproteinase-9

Introduction

Dengue infection is the most notable viral infection transmitted by mosquitoes, seen from the medical perspective and also the community health perspective. The incidence of dengue infection has increased significantly every year, from 0.05/100.000 in 1968 to 35-40/100.000 in 2013.[1] Indonesia is a dengue virus (DENV) endemic region and has experienced a 700-fold increase in incidence over the past 45 years.[2]

The hematological disorders known in dengue viral infection are temporary thrombocytopenia and leucopenia. The mechanism of neutropenia during dengue infection could be caused by bone marrow

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suppression or peripheral destruction. Changes in erythropoiesis is also observed in dengue infection, which may be caused by the bone marrow suppression affecting all of the hematopoiesis series. It is hypothesized that a combination of viral infection on hematopoietic progenitor cells, and the viral infection on bone marrow stromal cells and dengue specific T-cell activation, both releasing cytokines that suppress the bone marrow.[3,4]

Erythropoiesis suppression during dengue infection was also shown in the form of aplastic anemia by several case reports. Khoj et al reported aplastic anemia occurred after dengue infection and ended with bone marrow transplantation.[5] A study by Lora *et al*.[6] in Dominican Republic indicated that anemia related to the severity and mortality of dengue infection, found in 19% of patients and 32% of severe dengue infection with an Odd Ratio of 3 for mortality.Clinical manifestation of dengue infection in thalassemic patients was different, where they experienced the decrease of hemoglobin rather than hemoconcentration.[7]

Changes in erythropoiesis in dengue infection has not been extensively studied. Bone marrow examination is an invasive procedure and not recommended in dengue infection. A simple hematological parameter such as Immature reticulocyte fraction is expected to be able to indicate how active the erythropoiesis in the bone marrow is.[8]

Immature reticulocyte fraction (IRF) is a parameter reflecting the most immature reticulocyte fraction. This IRF parameter is simple and can be obtained directly from the automated hematology analyzer Sysmex XE-2100 (Kobe, Japan). The IRF reflects erythropoiesis directly and identifies erythropoiesis earlier than reticulocyte and hemoglobin. A study from Goncalo in hematological malignancy patients undergoing hematopoietic progenitor cells transplantation showed IRF as an earlier indicator for success than neutrophil and thrombocyte with two to four days of difference.[8-10] This study is aimed to order to observe whether erythropoiesis is really suppressed during Dengue infection.

Methods

This is a cohort study, using data derived from the Dengue-associated Endothelial Cell Dysfunction and Thrombocyte Activation (DECENT) research in the Department of Internal Medicine which ran from March 2011 to March 2012. The DECENT study was designed as a cohort study that recruitted patients presenting with clinical signs of symptomatic Dengue virus infection (SDVI) to Dr. Hasan Sadikin General Hospital in Bandung. Consecutive patients meeting inclusion criteria were enrolled and followed with daily clinical assessment, blood collection and, in a subgroup; assessment of plasma leakage until day 5 post-admission. Temporal changes on laboratory (thrombocytes and endothelial cells) parameters and plasma leakage during the infection were determined. Patients were asked to return for follow-up blood collection at >2 weeks (14–20 days) after discharge. Inclusion criteria are subject must be 14 years old or above, and clinical suspicion or confirmation of having DF or DHF/DSS according to WHO criteria. Exclusion criteria are pregnancy, clinical symptoms/signs of or known malignancy, known coagulation disorder, and any chronic diseases such as diabetes mellitus, chronic renal failure, hepatitis, auto-immune disorders, underlying hematological disease, using drugs causing myelosuppression and psychiatric disorders. Health Research Ethics Committee of the Dr. Hasan Sadikin General Hospital Bandung, Indonesia approved all legal and ethical aspects of the study (LB.04.01/ADS/EC/551/XII/2014).

The statistical test using the Friedmann test was used to examine the difference between the phases in dengue patients (4 groups), followed by a *post hoc* Mann Whitney test, the result is considered to be significantly different if the p value is <0.05.[11]

Results

There were 244 research subjects with a similar ratio of male and female, 56.6% of males and 43.4% of females, with the median age of 24 and IQR (interquartile range) of 14–67. The hemoglobin and hematocrit levels were normally distributed in every phase with a mean of 14.0±1.9 g/dL for hemoglobin and 41.1±5. % for hematocrit. Whereas, the leucocyte and thrombocyte levels were not normally distributed, with the leucocyte median of 5.100/mm^3 and IQR of 3.800/mm^3 to 6.600/mm^3, and the thrombocyte median of 78.000 mm^3 and IQR of 41.000/mm^3 to 177.000/mm^3. The baseline characteristics for each phase and control group (Table 1).

The IRF differences in various clinical phases of dengue infection and control group can be seen in Table 2 below. The median IRF for all the research subjects was 4.8% with

Table 1 Subjects Characteristics

Variable	Clinical Phase of Dengue Infection				Healthy Control (n=27)	p* value
	Fever Phase (n=13)	Critical Phase (n=77)	Recovery Phase (n=74)	Convalescent Phase (n=53)		
Sex (n, %)						
Male	8 (61.5)	46 (59.7)	42 (56.8)	32 (60.4)	10 (37.0)	0.292[c]
Female	5 (38.5)	31 (40.3)	32 (43.2)	21 (39.6)	17 (63.0)	
Age (year) median IQR	24 (20–28)	24 (19–33)	23 (19–33)	25 (20–34)	25 (22–31)	0.810[b]
Hb (g/dL) mean±SD	13.8±2.4	14.5±2.1	13.7±1.7	13.9±1.7	14.2±1.8	0.076[a]
Ht (%) mean±SD	40.0±6.1	42.2±5.8	39.9±4.8	41.5±4.3	42.3±4.7	0.040[a]
Leucocyte (x1000/mm^3) median IQR	3.3 (2.4–4.3)	4.0 (3.0–5.6)	5.0 (4.0–6.0)	7.1 (5.7–8.8)	7.0 (6.5–8.0)	<0.001[b]
Thrombocyte (x1000/mm^3) median IQR	66 (43–89)	36 (19–55)	94 (57–132)	265 (225–313)	293 (250–318)	<0.001[b]

*Note : analysis using a: ANOVA test, b: Friedman test, c: Chi Square test, significant if p<0.05

an IQR of 2.4–8.1%. The fever-phase group showed a median of 1.8% with an IQR of 0.5–2.85%. The critical-phase group showed a median of 3.6% with an IQR of 1.8–5.0%, while the median for the recovery-phase group was 7.05% with an IQR of 4.08-311.85%. The convalescent-phase group showed a median of 7.3 % with an IQR of 3.95–9.3%, and the healthy-control group showed a median of 4.1% with an IQR of 2.2–6.6%.

The result of the statistical test using the Friedman test on IRF (%) in various

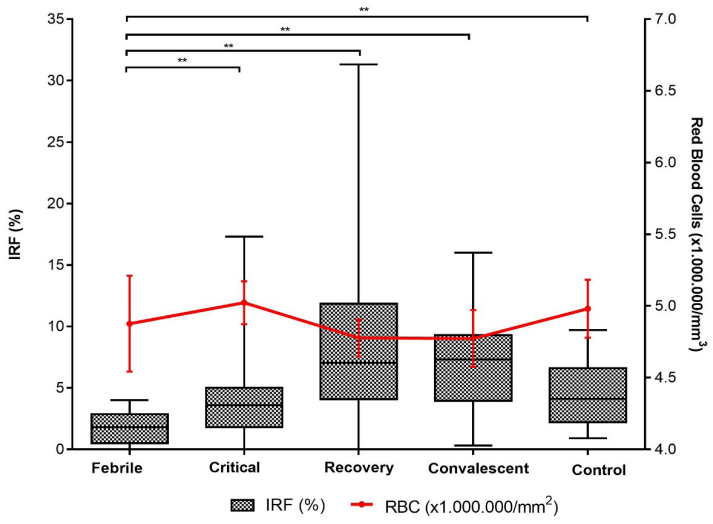

Fig. Boxplot of IRF in Clinical Phases of Dengue Infection

**Note : analysis using a post hoc Mann Whitney test shows significance with p<0.05

Table 2 Red Blood Cell Quantity and Immature Red Cell Fraction in Various Phases of Dengue Infection

Variable	Clinical Phase of Dengue Infection				Healthy Control n=27	p* value
	Fever Phase (n=13)	Critical Phase (n=77)	Recovery Phase (n=74)	Convalescent Phase (n=53)		
Red Blood Cells (million/mm^3) mean±SD	4.88±0.64	5.03±0.67	4.78±0.55	4.88±0.53	5.02±0.53	0.103[a]
IRF (%) median IQR	1.80 0.50–2.85	3.6 1.8–5.0	7.05 4.08–11.85	7.30 3.95–9.30	4.1 2.20–6.60	<0.001[b]
IRF Absolute (x1000/mm^3) median IQR	93 25–141	165 89–249	331 201–532	351 187–447	192 119–321	<0.001[b]

*Note : analysis using a: ANOVA test, b: Friedman test, c: Chi Square test, significant if p<0.05

clinical phases of dengue infection showed a significant difference with a p value of < 0.001. The statistical analysis was then followed by a *post hoc* Mann Whitney test to examine the difference between each group, and the difference is considered to be significant if p<0.05 (Fig).

The IRF (%) was lowest in the fever phase, then increased in the critical phase, reaching its highest in the recovery phase, and decreased in the convalescent phase. The IRF (%) in the fever phase was significantly different when compared to all the other phases and the healthy control group, with all the p value <0.05. The IRF (%) in the critical phase was significantly different when compared to the other phases in dengue infection (p<0.05), but not when compared to the healthy control group (p=0.218). The IRF (%) in the recovery phase was significantly different when compared to the fever phase, critical phase, and the healthy control group, but not when compared to the convalescent phase (p=0.629). The IRF (%) in the convalescent phase was significantly different when compared to the fever phase, critical phase, and the healthy control group (p<0.05). When compared to IRF (%), RBC counts were not significantly different among the phases of clinical dengue and also healthy control group.

Discussion

There were a total of 244 research subjects, with the median age 24 years and IQR (interquartile range) of 14–67 year. The number of male and female subjects was similar. The age and sex of the subjects in this reasearch were consistent with the report from *Pusat Data dan Surveilans Kementrian Kesehatan Republik Indonesia* in 2010 stating that cases of dengue infection in Indonesia occurred predominantly in the age group of more than 15 years old with the distribution of the cases nearly the same in both sexes.[1]

The hemoglobin levels in this research were not significantly different among the groups. A study by La Russa concluded that the bone marrow suppression in dengue infection happened rapidly, that even though the bone marrow suppression affected all hematopoietic series, the substantial erythrocyte reserve can compensate for the decrease in erythrocyte production.[3]

The result of the statistical test on hematocrit levels in every group showed a significant difference between the groups, with the highest hematocrit level in the critical-phase group. The increase in hematocrit levels corresponds to the hemoconcentration and plasma leakage that happens during the critical phase. Malavige and Malasit suggested that the increase in capillary permeability was caused by the involvement of mediators such as TNF-α, IL-2, IL-8, and VEGF that would disrupt endothelial cells permeability in vitro. The intensity of the immune response and the titer of plasma viremia are the strongest independent factors for plasma leakage.[12-13]

The leucocyte counts among the groups were significantly different. The results

showed that the lowest leucocyte count was found in the fever-phase group, then increased gradually according to the disease phase. A study by Simmons, Na-Nakorn and LaRussa stated that leucopenia and neutropenia were found in the early phase of the disease, and a bone marrow biopsy in the early phase of the disease (less than five days of fever) also showed more hypocellularity.[3,14]

The statistical test on the variable of thrombocyte level showed significant difference between the groups. The thrombocyte level started decreasing in the fever phase, with the lowest level found in the critical phase and started increasing again in the recovery and convalescent phases. The result was consistent with the pathogenesis of dengue viral infection where the suppression of bone marrow happens in the early fever phase and reaches its lowest point in the critical phase.[3]

The IRF in the fever phase was the lowest compared with other phases of dengue infection. The IRF started rising in the critical phase and kept rising in the recovery and convalescent phases.

The IRF in the fever-phase group was significantly different compared with the other groups. The low IRF reflected the bone marrow suppression occuring in the fever phase of dengue infection. This result was consistent with the bone marrow biopsy research done by Simmons et al showing that the onset of bone marrow suppression could happen not more than 12 hours after the infection. A study by Noisakran also showed that the dengue virus can reach the bone marrow compartment in a short period of time, confirming that bone marrow suppression occurs in the fever phase.[3,15]

The analytical result of IRF in the critical phase showed a significant difference compared with other groups, except the healthy-control group. This showed that the recovery of bone marrow suppression has started in the critical phase. A study by Noisakran showed that the number of dengue virus RNA reached a peak in day 1 to day 3 after the infection and then the number decreased, so the bone marrow suppression by dengue virus RNA lessened in the critical phase (day 4 of sickness). Noisakran concluded that bone marrow recovery ended in day 10 (afebrile period) even though the blood cell destruction (especially thrombocyte) in the periphery reached its peak (owing to antibody and complement clearance).[3,15] A research by Clark KB also stated that a bone marrow examination in day 4 to day 8 (critical phase) of sickness showed erythroid hyperplasia with maturation disruption.[14]

The IRF in the recovery-phase group was not significantly different compared to the convalescent-phase group. The IRF in the recovery-phase group and convalescent-phase group were higher than the critical-phase group and the healthy-control group. This result was similar with a bone marrow examination by Clark KB in day 10–14 of sickness that showed erythropoiesis hyperplasia without maturation disruption.[14]

The analytical result of IRF in the critical-phase group and healthy-control group using the Mann-Whitney test did not show any significant difference. The pathogenesis of dengue infection states that thrombocyte and leucocyte reach the lowest level in the critical phase, but the same thing did not happen to the erythrocyte in this reasearch, represented by the IRF. This result was similar to research by Clark and Noisakran which showed that bone marrow suppression started its recovery in the critical phase, characterized by erythropoiesis hyperplasia with maturation disruption.[3,14-15] The increase in erythropoiesis is usually followed by an increase in erythropoietin. The life span of reticulocytes in the circulation also increases for up to three days or even more, due to the release of 'stress or shift' reticulocytes from the bone marrow and the acceleration of erythroid differentiation. 'Stress or shift' reticulocytes from the bone marrow have a large amount of RNA in their cells. The population of existing reticulocytes can not only be counted, the RNA content according to its maturity level needs to be assessed as well, and this has a significant clinical application in evaluating the erythropoiesis activity.[16]

The comparison between IRF in the critical-phase group and healthy-control group did not show significant difference, which shows that bone marrow of dengue patients in the critical phase is not different from the bone marrow of healthy people in general. This result confirmed that thrombocytopenia occuring in critical phase of dengue infection is caused by cell destruction in the periphery, due to the antibody and complement clearance.[3]

The previous retrospective study in 26 parvovirus B-19 infection in 119 sickle cell disease patients found that IRF is highly specific to detect severe aplasia. Increasing IRF predicts reticulocyte recovery in reticulocytopenia patients and could have utility in clinical decision making such as whether to transfuse packed red blood cells.[17]

In conclusion, this study was the first study describing IRF in multiple phases of dengue disease. There was an erythropoiesis difference between the phases of dengue infection. Bone marrow suppression for erythropoiesis reached the lowest point in the fever phase and started recovering in the critical phase. Erythropoiesis in the critical phase was not different from the healthy control.

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Pulmonary Embolism in High-Risk Patients: How to Select Standard Imaging and Management Strategy?

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2142
IJIHS. 2021;9(1):30–35

Received:
September 21, 2020

Accepted:
March 30, 2021

Abstract

Objective: To describe the use of computed tomography pulmonary angiography (CTPA) for diagnostic purposes and percutaneous catheter-directed thrombolysis (PCDT) as a treatment choice for high-risk pulmonary embolism (PE) patients.

Methods: This case report describes a case of an elderly female presented with dyspnea, cough, fever, and chest pain. No significant medical history was identified.

Results: CTPA was conducted and showed multiple thrombus with significant stenosis in several branches of pulmonary artery. Initial anticoagulation was administered without delay. Patient then underwent PCDT to remove the thrombus. No post intervention symptom and systemic complications were noted.

Conclusions: Computed tomography pulmonary angiography is useful as the standard imaging modality to help evaluating suspected pulmonary embolism. Percutaneous catheter-directed thrombolysis is indicated to treat high-risk patients with high risk of bleeding.

Keywords: Computed tomography pulmonary angiography, elderly people, high-risk pulmonary embolism, pulmonary embolism, treatment

Introduction

Pulmonary embolism (PE) is a life-threatening thromboembolic event.[1] The incidence of PE has been growing and has reached the rate of 65 cases in 100.000 population.[2] Patients may experience various unspecific symptoms. Acute dyspnea is the most common symptom in PE. Chest pain is commonly associated with coronary events, but patients with pulmonary embolism may also experience chest pain with elevated levels of troponin. Unspecific symptoms such as fever may also appear although fever has no impact on disease severity or prognosis.[3,4] The clinical condition could go from low risk to high-risk with complications. Therefore, early diagnosis is important to determine the treatment strategy and prevent the mortality of the patient.[5] Imaging modality could be useful to help establish the diagnosis. Various imaging modalities are available for evaluation of PE includes chest radiographs, echocardiography, computed tomography (CT) pulmonary angiography (CTPA), CT venography, magnetic resonance (MR) pulmonary angiography (MRPA), and ventilation/perfusion scan. Each modality has their own characteristics and diagnostic role.[6] The purpose of this article is to describe the use of CTPA as the standard imaging modality to help establish the diagnosis of pulmonary embolism and its treatment based on patient's clinical condition.

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Case

The case describes A 70-years-old female who was admitted to our hospital due to dyspnea since 7 days before admission and became worsen, accompanied by cough, intermittent fever, and chest pain after 3 days since the initial onset of dyspnea. The patient was ill with GCS E4V5M6. The diagnosis of pleuropneumonia was made at the beginning with pulmonary embolism as a differential diagnosis, supported by infiltrates appearance in chest computerized tomography (CT) scan. There were not any significant past medical history. The physical examination showed rhonchi in both lungs and the cor was normal. Our patient then had a cardiac arrest and we conducted cardiopulmonary resuscitation (CPR). The rhythm was shockable and we shocked the patient. The return of spontaneous circulation (ROSC) was achieved. Due to the suspicion of PE, we administered enoxaparin. After the international normalized ratio (INR) had been achieved, we also administered warfarin.

Electrocardiography (ECG) and laboratory tests were done. The ECG (Fig. 1) showed a deep S wave in lead I, Q wave in lead III, and an inverted T wave in III. T-wave inversions in precordial leads also appeared. The blood cell count was normal, arterial blood pH was 7.39, pO_2 250 mmHg, pCO_2 30 mmHg, HCO_3 18 mEq/L, and base excess was -5 mEq/L. Another laboratory test showed an increased high-sensitivity troponin T (39.79 ng/L) and NT-proBNP (11178 pg/mL).

The patient then underwent a computerized tomography pulmonary angiography procedure. The CT showed thrombus in the right pulmonary artery truncus, anterior truncus of the right pulmonary artery, and right interlobar pulmonary artery (Fig. 2 and Fig. 3). Thrombus was also shown in the left interlobular pulmonary artery (Fig. 4). There were also significant stenosis in the right pulmonary artery truncus, right pulmonary artery anterior truncus, and left interlobular pulmonary artery (Fig. 2-Fig. 4).

The patient was given systemic thrombolysis and underwent a percutaneous catheter-directed thrombolysis (PCDT) procedure, and the symptoms had improved (Fig. 5). Consent was given to the patient for this procedure and case report publication.

Discussion

Pulmonary embolism is a condition that occurs because of a blood clot that travels to the pulmonary vessel. PE could be misdiagnosed at the beginning because the other diseases can mimic the symptoms of PE in the elderly.[7] PE is the most common type of cardiovascular

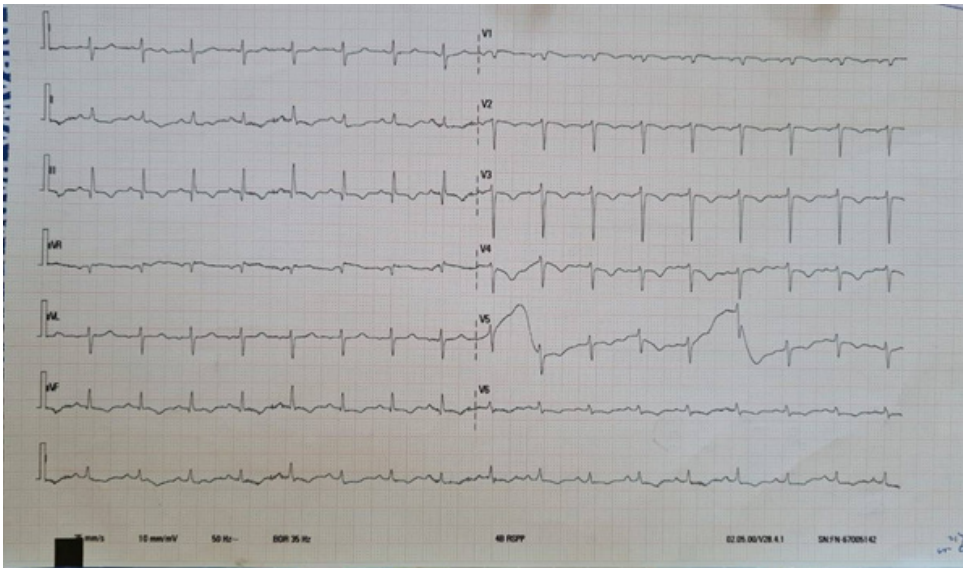

Fig. 1 ECG of the Patient Showed S1Q3T3 (S wave in lead I, W Wave and Inverted T Wave in lead III) Pattern and T-inverted Waves in Precordial Leads

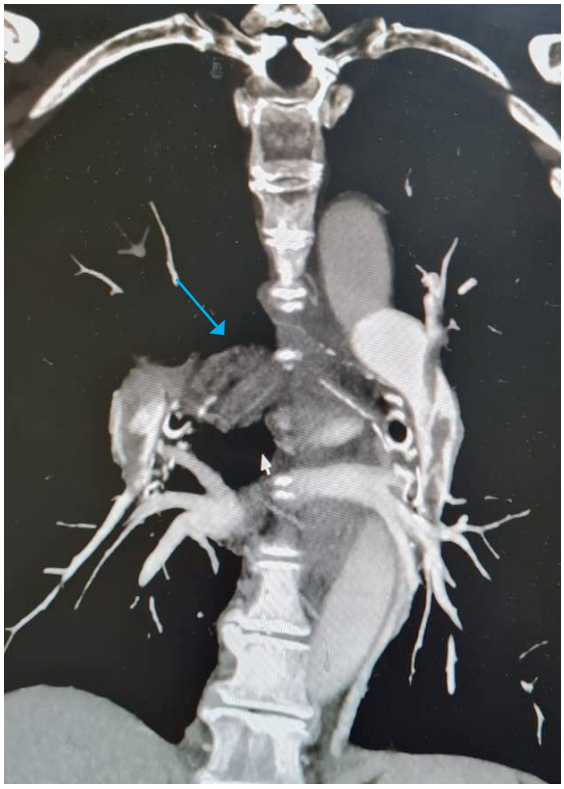

Fig. 2 Thrombus in Right Pulmonary Artery Truncus with Significant Stenosis (Blue Arrow)

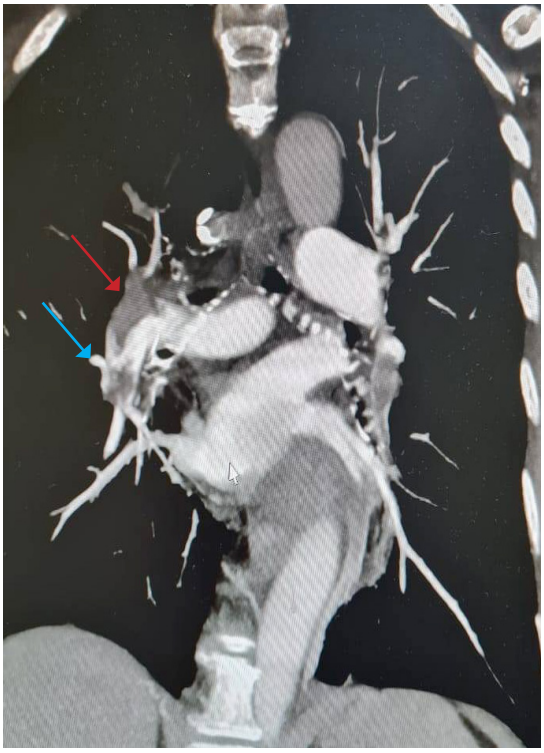

Fig. 3 Thrombus in Right Interlobar Pulmonary Artery (Blue Arrow) and Anterior Truncus of Right Pulmonary Artery with Significant Stenosis (Red Arrow)

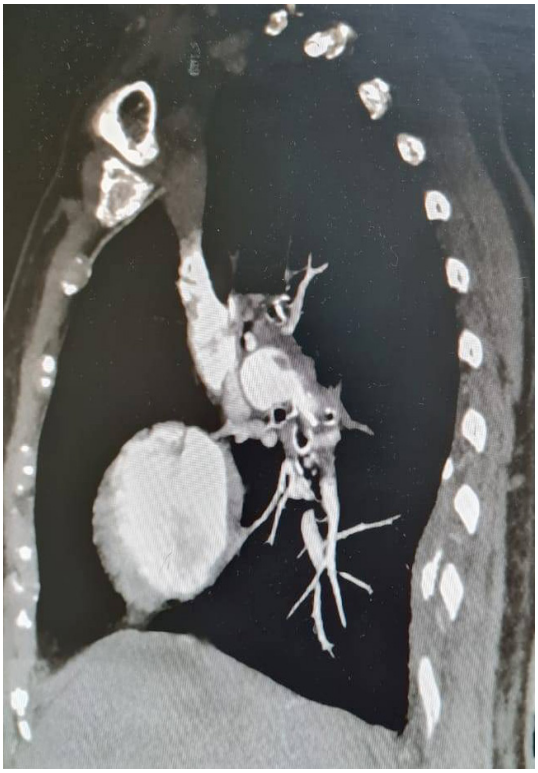

Fig. 4 Thrombus in Left Interlobular Artery at Posterior Basal Segment with Significant Stenosis (blue arrow)

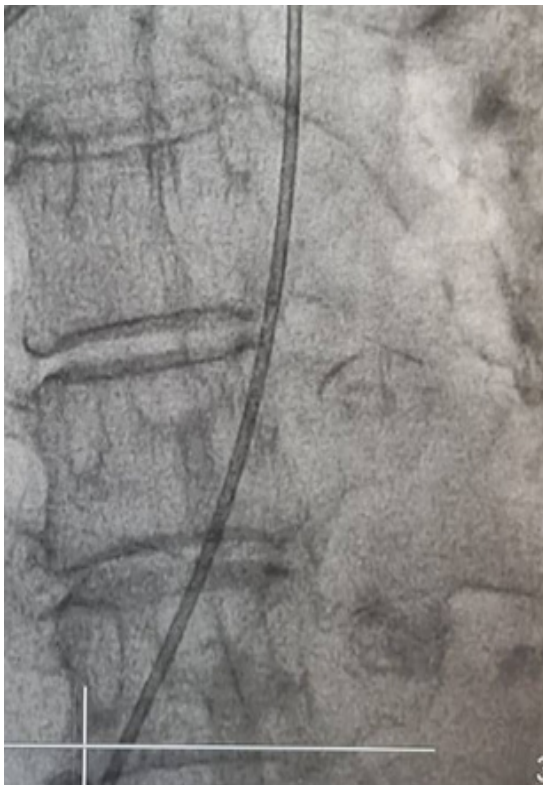

Fig. 5 Percutaneous Catheter-Directed Thrombolysis Procedure in Our Patient

disease after coronary artery disease and stroke. The obstruction in the pulmonary vessels could manifest in right ventricular failure. Thus, early diagnosis is very important because PE could cause sudden death within 2 hours after presentation, and also associated with a quite high mortality rate, 30% if it is not treated.[8] Several risk factors could make someone more susceptible to experience PE, such as older age (>60 years old), history of venous thromboembolism events, trauma, previous major surgery, malignancy, coagulation disorders, and hormonal therapy.[9]

The most common symptoms that patients may experience are dyspnea (~92% of all patients with PE), pleuritic chest pain (49%), and also cough (20%). The symptoms occur due to disruption in pulmonary circulation, increased pulmonary arterial pressure, and disturbance in coronary circulation.[10,11] In this case, our patient presented with several common symptoms of PE with older age as the only known risk factor. Our patient also experienced a fever. A study explained that fever (38°C -38.5°C) may present in pulmonary embolism and is associated with higher morbidity and clot burden. The mechanism of fever in PE is still unknown but may be related to inflammation cascade due to vascular irritation, tissue injury, or atelectasis.[12]

Clinical signs that refer to PE should be assessed to establish the diagnosis of PE. CTPA is the standard imaging modality with high sensitivity and specificity. The finding in CTPA are filling defects (gray) in pulmonary arteries (white). CTPA may be contraindicated in patients with kidney disease, pregnancy, or allergy to contrast. Patients who are contraindicated to undergo CTPA may undergo ventilation/perfusion lung scanning.[13]

Risk stratification is essential to do because it will determine the treatment strategy. The presence of shock, right ventricular dysfunction, and biomarkers elevation are signs of high-risk PE.[6] The patient had a cardiac arrest suggesting the presence of shock. The ECG of our patient showed the S1Q3T3 pattern (acute right ventricle dysfunction).[14] Further evaluation of RV function can be done by echocardiography. Some echocardiography findings in PE are RV hypokinesis/dilatation, RV/LV ratio end-diastolic diameter >1, RV end-diastolic diameter >30 mm, D-sign (ventricular septum pushed towards the LV), increased pressure of pulmonary artery, and inferior vena cava dilatation.[15,16]

This study also conducted laboratory tests to determine the NT-proBNP and Troponin T levels in our patient. The result showed the elevation of both biomarkers. Elevation of these biomarkers could show right ventricular dysfunction and have roles in risk stratification and prognostic indicators in PE cases.[17]

Management of pulmonary embolism is based on the severity of the disease. Our patient was classified into high-risk PE. The management of high-risk PE should be started with anticoagulant administration without delay, even while waiting for another diagnostic test result. We administered enoxaparin (LMWH) to our patient as the initial anticoagulant. LMWH was chosen instead of UFH because it carried a reduced risk of major bleeding and heparin-induced thrombocytopenia.[18] High-risk PE is an absolute indication for thrombolytic treatment. Thrombolysis is beneficial in patients with the onset of symptoms range for 6-14 days and it can significantly reduce the mortality and recurrence of PE in the high-risk patients. Thrombolytic therapy can be done by administering systemic thrombolysis or by using catheter-directed thrombolysis (CDT). While systemic thrombolysis is effective as a treatment, it is also associated with a higher risk of severe bleeding (9.9%). Thus, CDT can be done as an alternative treatment in patient who has a high risk of bleeding, such as an elderly patient. CDT is also indicated in a patient with a shock that can cause death, before systemic thrombolysis has its effect.[19,20] In conclusion, the risk of experiencing PE is increased in the elderly. Proper diagnosis and treatment could prevent mortality. CTPA is useful to help make the diagnosis in suspected PE patient, so the clinician could determine the treatment strategy. PCDT is indicated in high-risk PE patient with a life-threatening condition that needs prompt treatment.

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Congenital Complete Heart Block in Young Women

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2142
IJIHS. 2021;9(1):42–48

Received:
September 21, 2020

Accepted:
March 30, 2021

Abstract

Objectives: To present a rare case of Congenital Complete Heart Block (CCHB) in the setting of post-cesarean delivery of an asymptomatic young patient.

Methods: A 30-year-old female patient complained of sudden weakness after C-section delivery with spinal anesthesia. She presented a slow heart rate and Complete Heart Block (CHB) on electrocardiogram (ECG). After one week of observation, the ECG still presented a CHB condition. A permanent pacemaker (PPM) with DDDR mode was then installed for this patient.

Result: The etiology of CHB, especially at a young age, is unclear, hence challenging. A patient with a CCHB is difficult to diagnose, especially without any previously related symptoms. This abnormality is usually detected during routine screening not related to cardiovascular disease. The patient in this case study presented an ECG of persistent CHB from the time this patient was admitted until one week after observation. The echocardiography showed normal results. Other modalities to confirm diagnosis and evaluate the prognosis of a CCHB should be done.

Conclusion: Establishing the etiology of CHB in young patients is challenging. The implantation of PPM is needed because the condition is permanent, regardless the etiology. However, implanting a permanent pacemaker is not always an easy decision, especially in young patients.

Keywords: Complete heart block, congenital, young

Introduction

Heart block is a disturbance of impulse conduction that can be permanent or transient, depending on the anatomic or functional impairment. It must be distinguished from interference, a normal phenomenon that is a disturbance of impulse conduction caused by physiologic refractoriness resulting from inexcitability secondary to a preceding impulse. Interference or block can occur at any site where impulses are conducted, but they are recognized most often between the sinus node and atrium (SA block), between the atria and ventricles (AV block), within the atria (intra-atrial block), or within the ventricles (intraventricular block).[1,2]

Complete heart block can be acquired or congenital. It can occur due to multiple pathological conditions. The etiology of complete heart block, which ensues in the young population, was only identified in approximately half the patients, in whom complications to cardiac surgery or congenital complete heart block were the most common aetiologies. The acquired CHB occurs due to various reasons: medicines, acute myocardial infarction, chronic ischemic heart disease, degenerative diseases, rheumatic diseases, infiltrative processes, neuromyopathy, infectious diseases, iatrogenic, and AV blocks

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mediated by vagal processes. In some rare cases, spinal anesthesia can cause CHB. Congenital heart block that occurs after spinal and epidural anesthesia may combine several processes, such as drugs, iatrogenic, and vagal.[1,3-7]

The incidence of CCHB varies from 1 in 15,000 to 1 in 22,000 live births.[1] The signs and symptoms of patients with CCHB depend on the baseline ventricular rate and underlying structural defects. Patients may be asymptomatic until cardiac decompensation begins to occur in adulthood.[8] In this case report, the author will discuss etiology of CCHB in a young post partum patient and diffrentiate it from other causes of CHB.

Case

A thirty-year-old female (P1, A0) was referred from a satellite hospital and consulted in the emergency room due to a complete heart block after Caesarean delivery with spinal anesthesia. She complained of progressive generalized fatigue a few hours after Caesarean delivery, so that she was unable to perform a regular activity. There were no accompanying neurological symptoms, heart failure, nor a history of hypertension.

The patient's heart rate was reported to be slow by her husband, with no significant symptoms before the procedure. Spinal anesthesia was performed using Bupivacaine 10 mg and Fentanyl 25 U. The procedure went smooth with 2900 gram healthy baby girl was delivered. Shortly after the delivery, the patient has hypotension and bradycardia. Resting ECG showed a complete heart block with QRS duration 0.08 s and prolonged QTc of 516 ms. Soon thereafter, she was referred to Hasan Sadikin General Hospital for Temporary Percutanues Pacemaker (TPM).

On arrival in the emergency room, the vital signs showed a slow heartbeat of 40 beats per minute and the blood pressure 120/80 mmHg. Her physical examination was unremarkable. The ECG showed CHB with QRS duration 0,08 s and prolonged QTc of 574 ms. Her chest X-ray examination revealed an enlarged heart. Her blood examination showed; hemoglobin 12.3 g/dL, leukocyte 7,200 /mm^3, thrombocyte 342,000, urea 52 mg/dL, creatinine 0.98 mg/dL, sodium 137 mg/dL, potassium 4.2 mg/dL, calcium 4.81 mg/dL, magnesium 2.1 mg/dL. The transthoracic echocardiogram showed normal heart chambers, normal valves, and normal systolic and diastolic functions. There was no LV or RV thickening, no "granular sparking" or "speckling," and aneurysm.

Based on the data above, the patient was diagnosed with a CHB, possibly due to spinal anesthesia. We still investigated the other cause of the CHB. We suspected a congenital involvement as a cause due to the previous history of slow heart rate but undocumented ECG. We then put her on a temporary pacemaker. Afterward, she was transferred to the High Care Cardiac Unit and was monitored intensively for one week. However, the ECG showed persistent CHB,

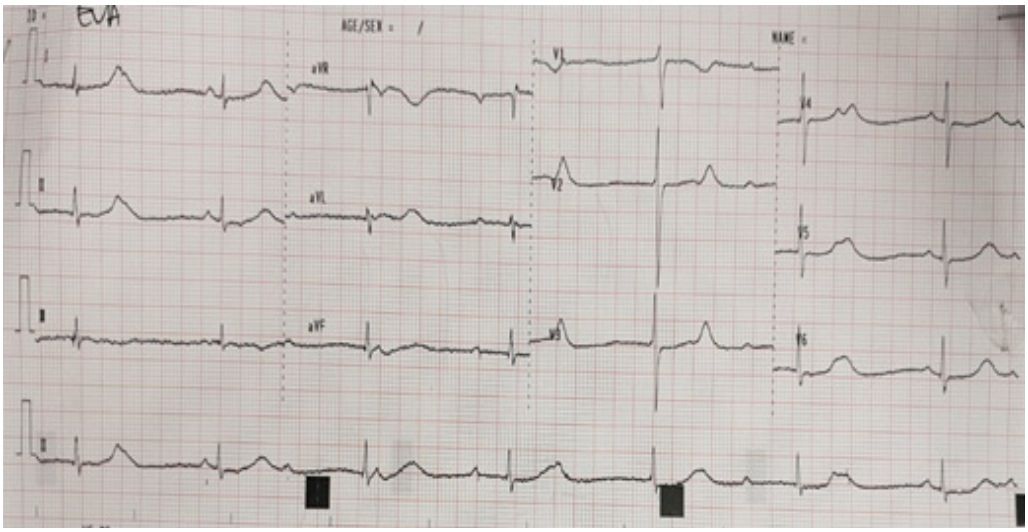

Fig. 1 ECG with Complete Heart Block

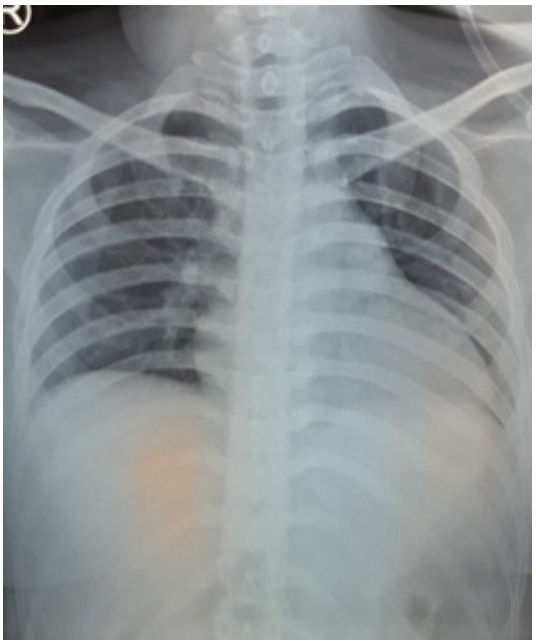

Fig. 2 Chest X-Ray

despite the already diminished effect of the anesthetic drug. Doctors have excluded spinal anesthesia as the etiology and perform workup for other etiology such as congenital or autoimmune. Unfortunately, the patient's mother was not present, so we could not examine immunoassays for SSA/Ro or SSB/La antibodies, but this patient did not have any signs and symptoms of autoimmune disease. Patient heart rate persists below 50 beats per minute and still with prolonged QTc of 515 ms. Based on the recommendation by guideline, we decided to perform a permanent pacemaker (PPM) installation on the patient and programmed with DDDR mode without any complications. The patient had provided informed consent for scientific publication and agreed to be published. This case report was conducted from January 2019 to February 2019.

Discussion

The etiology of CHB was unclear, hence challenging. A complete heart block in this patient was initially suspected of spinal anesthesia complication after the Caesarean delivery procedure. In a case report by Joseph et al.[4], they said that they recorded the systemic symptoms after spinal anesthesia injection after 4 minutes, and a CHB was reported several minutes afterward. The reported time needed for the heart's impulse to return to sinus rhythm after CHB was 4 minutes. Another case report by McHugh *et al*.[5] said that 5 minutes after subarachnoid injection, the non-specific symptoms were noted, and a CHB was revealed. It sustained first-degree heart block for 6 hours after subarachnoid injection, and afterward, the rhythm returned to sinus rhythm.

In this patient, we rejected the possibility of complications of spinal anesthesia as the cause of the heart block because the CHB persisted after one week. In contrast, most CHB caused by spinal anesthesia would return to sinus rhythm after several hours. This patient complained of symptoms of CHB after the Caesarean delivery had finished, where most of the spinal anesthesia complications would be seen several minutes after the spinal anesthesia drug was injected.

The etiologies of CCHB include the following: autoimmune antibodies, structural heart abnormalities due to congenital heart disease (e.g., congenitally corrected transposition of the great arteries, endocardial cushion defects), idiopathic familial CCHB.[6,7,9] CCHB due to the autoimmune disease usually begins in utero, though clinical detection may occasionally be postponed until after birth or during early childhood.[10] In many cases, the block is a complete heart block. The mechanism is due to damage to the development of specialized conduction tissue from passive transplacental passage of maternal autoantibodies to Ro/SSA and/or La/SSB intracellular ribonuclear proteins.[9]

The etiology possibility of CHB in this patient due to congenital cause is getting more likely because the etiology of CHB at a young age, such as cardiomyopathy, infection, infiltrative disease, and ischemic heart disease, had been excluded based on the clinical history and examinations that have been carried out. The patient reported no prior history of complaints. This study found several data that support this condition. Baruteau *et al*.[8] and Bordachar *et al*.[11], said that some people with CHB are asymptomatic with bradycardia and detected only during routine screening. Patients may be asymptomatic until cardiac decompensation begins to occur in adulthood. It raised suspicion of CCHB as the mechanism of the slow heartbeat in this patient.

Postnatally, neonates and young children present in a wide variety of different ways. Some are asymptomatic with bradycardia and detected only during routine screening. Others may present with nonspecific symptoms, such

as poor growth, abnormal tiredness, sleep disturbance, or frequent nightmares. Syncope, heart failure, or sudden death may be the first manifestation of congenital AV block in the absence of previous symptoms and signs of cardiovascular disease.[11]

Congenital CHB is related to congenital heart defects. In various series of fetal CCHB, 30 to 53% of cases have associated congenital heart disease. Various forms of congenital heart disease are related to abnormalities in the development of AV conduction tissue, such as L-looped transposition of the great arteries (L-TGA), Endocardial cushion defects, and syndromes with simple atrial septal defects. Anatomic disruption between the atrial musculature and peripheral parts of the conduction system and nodoventricular discontinuity are two common histologic findings.[2,12]

Idiopathic familial CCHB — Non-immune CHB in patients with a structurally normal heart has also been described as an idiopathic disorder with a strong familial tendency. In a retrospective cohort of 141 children with AV block diagnosed in utero or up to age 15 years (51% female, 84% asymptomatic, 71% with CHB on presentation, with an additional 21% progressing from incomplete to CHB), 112 patients (79%) received permanent pacemakers, most prophylactically in asymptomatic patients (70 of 112 patients [63%]).[13]

There were several modalities that can be utilized to diagnose CCHB. Electrocardiography can be used used to diagnose arrhythmia and the type of heart block. An electrophysiology study can be performed to locate the level block in the conduction system. The treadmill stress test was needed to evaluate functional capacity. Holter monitoring can be conducted to determine how heart rate and rhythm vary with activities of daily living. Immunoassays for SSA/Ro or SSB/La antibodies. Lastly, echocardiography can be used to determine structural problems.[8,11]

Patients with CCHB may undergo routine 12-lead ECG, echocardiography, holter monitoring, electrophysiology studies, and treadmill testing to determine the effects of the disease process. The results of diagnostic tests are not predictive of who will die from CCHB, but the results do indicate risk factors and can be used to determine which patients should receive a pacemaker. Resting heart rate decreases with age in patients with CCHB during infancy and childhood, and heart rates less than 50/min are associated with signs and symptoms and increasing mortality.[14]

In nearly all cases, the diagnosis of complete heart block can be made by obtaining a surface ECG, ideally a full 12-lead ECG, but sometimes a single-lead rhythm strip is adequate if a full 12-lead ECG cannot be obtained. The diagnosis is usually suspected when a slow pulse is detected, and heart block is confirmed by ECG or by ambulatory ECG monitoring.[14,15]

As mentioned in several previous studies, a CCHB could be initially recognized from routine ECG records. In our patient, we suspected having a complete heart block by ECG recorded after the Caesarean delivery procedure, even though there was no previous record of such findings. The recorded ECG of this patient revealed a complete heart block with prolonged QTc of 516 ms and 574 ms. This is in accordance with the conditions described in previous studies that CHB might have prolonged QTc. Seven percent of the patients were identified as having a prolonged QT interval (corrected QT interval 450 ms) at the time of presentation in the study by Michaelsson et al.[14]

In other ECG evaluations, our patient had a narrow QRS complex of 80 ms. The width of the QRS complex is used to infer whether hemodynamically unstable cardiac rhythms may develop. A ventricular rhythm with a wide complex (>120 ms) and a prolonged QTc (>450 ms) in patients with CCHB is an unfavorable prognostic sign because it may be related to underlying myocardial damage.[14] Prolonged QTc is associated with congenital CHB and occurs in approximately 15% to 22% of patients.[16] In multiple studies, a greater percentage of patients with congenital CHB and QTc prolongation greater than 450 ms had signs and symptoms related to the CCHB or suddenly died than did CCHB patients without QTc prolongation.[8] Michaelsson *et al.*[14], described the electrocardiographic characteristics in a large population of patients with congenital AV block; the mean heart rate was 41 beats/min, the heart rate usually decreased as the child grew older, and they observed a broad complex escape rhythm in 10% of the patients.

Two mechanisms have been proposed for the development of QT prolongation in patients with CCHB. First, the conduction disorder and resultant bradycardia may be the initial phenomenon that subsequently leads to the development of altered repolarization. This is supported by data from animal models of chronic complete heart block. Second, patients with congenital AV block who develop QT

prolongation may manifest phenotypic latent congenital long QT syndrome.[11]

In prenatal conditions, echocardiography may be helpful. With fetal echocardiography, a high proportion of autoimmune-mediated complete heart block cases are now identified in utero (in populations where routine fetal echocardiography is performed). The finding may be an incidental finding. Fetal echocardiography remains the standard gold method for diagnosing congenital CHB. The diagnosis is made by establishing atrioventricular dissociation by using M mode or Doppler echocardiographic techniques. Reference values have been defined, and surveillance protocols have been designed to be implemented between 16 and 24 weeks of gestation, the period during which the fetus is at the highest risk of developing complete heart block.[11] The patient had normal echocardiography results without structural abnormalities.

The suspicions of congenital complete because there was no symptom nor chronic HF symptoms and no history of autoimmune disease. This condition might be due to idiopathic familial CCHB. Anti Ro/La negative cases constitute around 30% of all congenital CHB.[17] Fetal conduction tissue injury caused by transplacental exposure to maternal autoantibodies related to autoimmune disease is responsible for 70 to 90 percent of cases CCHB.[15] As stated by Bordachar et al.[11], he family history of autoimmune disease, especially in the patient's mother, was possible in a patient with congenital AV Block. Once heart block has been diagnosed, the mother should be screened for evidence of connective tissue disease. Immunoassays for SSA/Ro or SSB/La antibodies should be performed.[11] Unfortunately, we did not perform any examinations to prove it in this patient.

The incidence of CCHB is 2% in maternal anti-Ro/SSA antibody positivity cases, 3% when both anti-Ro/SSA and anti-La-SSB are positive. Isolated CCHB or CCHB with a structurally normal heart is frequently associated with Ro/SSA and La/SSB maternal autoantibodies. In this series of cases, all the mothers were positive for ANA, SS-A (Ro), antibodies, and SS-B (La) antibodies, except in the first case where SS-B (La) antibodies were negative. Pregnant women whose sera contain anti-Sjögren's syndrome A (SSA)/ Ro antibodies (in the presence or absence of anti-SSB/La antibodies) have a 1–7.5% risk of having a child with third-degree CHB.[18] Thus, in cases of children with CHB, the patient's mother should be examined for anti-Ro / SSA and anti-La-SSB.

Despite the conduction disorder, many patients have a normal exercise treadmill evaluation in terms of performance.[11] Treadmill exercise testing is done mainly to evaluate functional capacity.[8] In patients with CCHB without structural heart disease, up to 90% have normal results in exercise treadmill tests.[14,16] In this case treadmill test was not performed.

This patient has eventually implanted a PPM with DDDR mode. This was following the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay:[19] in adults with a congenital complete atrioventricular block with any symptomatic bradycardia, a wide QRS escape rhythm, mean daytime heart rate below 50 bpm, complex ventricular ectopy, or ventricular dysfunction, permanent pacing is recommended. A similar statement was also mentioned in the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy:[20] pacing is indicated in a high degree and complete heart block in symptomatic patients and in asymptomatic patients with any of the following risk conditions: ventricular dysfunction, prolonged QTc interval, complex ventricular ectopy, wide QRS escape rhythm, ventricular rate < 50 b.p.m., ventricular pauses > three-fold the cycle length of the underlying rhythm.

A patient with CCHB was hard to detect, especially without any previous related symptoms. This abnormality was usually detected from routine screening or when ECG was performed for other complaints related to the non-cardiovascular disease. Other modalities to confirmed diagnosis and evaluate the prognosis of CCHB could be done.

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Correlation between MMP-9 Level and Diastolic Dysfunction in Concentric Left Ventricular Hypertrophy Patients

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2175
IJIHS. 2021;9(1):1–6

Received:
October 18, 2020

Accepted:
March 30, 2021

Abstract

Objective: To establish the relationship between plasma matrix metalloproteinase (MMP)-9 levels and diastolic functional abnormalities using the E/e' measurement in concentric type Hypertensive Heart Disease (HHD) patients.

Methods: A cross-sectional study was conducted from November 2014 to January 2015 in population with hypertension and concentric Left Ventricular Hypertrophy (LVH). Diastolic function was assessed with E/e' measurement using echocardiography. The relationship between the two variables was analyzed using Spearman correlation.

Results: Thirty-nine subjects (14 males, 35.9%) with the average relative wall thickness of 0.7(±0.15), average body weight of 63.45 (±12.97) kg, average height of 155.51 (±7.12) cm, average body mass index of 26.23 (±5.08) kg/m^2, and mean age of 55 (±10) years were fit to be included in the analysis. The median systolic blood pressure was 140 (110–220) mmHg while the median diastolic blood pressure and median left ventricular mass index were 80 (70–110) mmHg and 119.24 (103.05-205.69) g/m^2, respectively. The median MMP-9 was measured at 108 (4–460) ng/mL and the median E/e' was 10.99 (6.2-20.42). There was a significant positive correlation between MMP-9 and E/e' (r=0.416, p=0.004).

Conclusion: There is a significant moderate positive correlation between the MMP-9 level and diastolic dysfunction in concentric LVH patients.

Keywords: Diastolic dysfunction, hypertensive heart disease, left ventricular hypertrophy, matrix metalloproteinase-9

Introduction

Hypertension is a major risk factor for coronary artery disease (CAD), stroke, and heart failure.[1] The risk of heart failure in hypertensive patients is threefold higher than those without hypertension.[2] Hypertension is one of the most prevalent diseases in the world. The prevalence of hypertension in >25-year-old worldwide is 40.6% in men and 35.8% in women. The prevalence varies based on geographical location as well. In Southeast Asia, the prevalence of hypertension is approximately 37.3% in men and 34.9% in women.[3] Based on the 2013 Indonesia Basic Health Research (Riset Kesehatan Dasar/ RISKESDAS), the prevalence of hypertension is 25.8%, with West Java sits on one of the top four most prevalent province with hypertension in Indonesia.[4]

Non-communicable diseases contributed to 63% of mortality worldwide in 2008 (36 out of 57 million deaths), mostly caused by cardiovascular diseases.[5] Hypertension is One of many major cardiovascular disease risk factors. In Indonesia, hypertension related to 20-25% of all coronary artery disease cases

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and 36-42% of all strokes.[6]

Prolonged hypertension may injure the cardiovascular system, with secondary damages to the brain, eyes, and kidneys. The presence of target organ damage can also impact therapeutic strategies, targeted blood pressure, and specific recommended medications.[1,7] Chronic hypertension may lead to remodeling of the heart. Cardiac remodeling involves changes in genomic, cellular, and interstitial levels that can be clinically evaluated as alterations of the heart's shape, size, and function.[8] Concentric hypertrophy is the most common pattern of hypertrophy found in hypertension.[8] Cardiac remodeling may also affect the heart physiology and is manifested as diastolic dysfunction. Gold standard assessment of diastolic function involves invasive measurement, but recently has been replaced by non-invasive techniques, with one of the methods is echocardiography.[9] The method for assessing diastolic dysfunction recommended by the European Society of Cardiology (ESC) is the examination of the ratio between trans mitral inflow Doppler and Tissue Doppler Imaging (TDI) early diastolic velocity (E/e '). E/e ratio of ≥13 was related to increased risk of cardiovascular event and was independent of left ventricular mass and relative wall thickness in hypertensive patients.[7,10]

Plasma matrix metalloproteinase (MMP)-9 is one of the collagen turnover markers that is widely used as an indicator of ventricular remodeling in cases of heart failure.[11-13] There is a lot of studies done about MMP-9 and ventricular remodeling, both in pre-clinical studies and clinical studies. However, there are not many studies on the relationship of diastolic dysfunction with MMP-9 and these studies have had different results in terms of the relationship between MMP-9 levels and diastolic function abnormalities. This study aims to analyze the relationship between MMP-9 levels and diastolic function abnormalities.

Methods

A cross-sectional study was conducted in Bandung from November 2014 to January 2015 with ethical clearance from dr. Hasan Sadikin General Hospital. The subjects in this study included patients clinically diagnosed with concentric-type left ventricular hypertrophy HHD, age >18 years old in Out-Patient Department dr. Hasan Sadikin General Hospital. Consecutive sampling was used. The sample size (n) in this correlation analysis study was determined by the sample and power calculation program with the calculation of the test for one correlation. The minimum number of samples that must be obtained is 30 samples. Exclusion criteria include patients with atrial fibrillation, aortic stenosis, CAD, diabetes mellitus (DM), cancer, hypertrophic obstructive cardiomyopathy, mitral stenosis, coarctation of the aorta, chronic kidney disease (CKD) stage ≥3, and septic shock.

The independent variable of this study is the MMP-9 plasma level, while the dependent variable is diastolic dysfunction (E/e'). MMP-9 levels were assessed from peripheral venous blood sampling on the same day of echocardiography examination. The blood was drawn and put into a tube containing Ethylene-Diamino-Tetraacetic Acid (EDTA) and then centrifuged at 4°C. Plasma component was isolated and kept frozen at -70°C for further storage. MMP-9 plasma levels were examined using Enzyme-Linked Immunosorbent Assay (ELISA), expressed in ng/mL units.[14] Diastolic dysfunction was assessed by echocardiography using a Vivid 7 echocardiography machine. Parameters were measured using the mitral inflow ratio to tissue Doppler imaging method or the E/e' ratio. E/e' values parameter is obtained from the mean values of E/e' septal and E/e' lateral.[7,10]

A standard echocardiographic examination is performed by a technician. The results were then confirmed by a cardiologist specialized in echocardiography. Blood samples were drawn after echocardiographic examinations on the same day by trained nurses using a tourniquet and 3cc syringes. All samples were stored collectively at the Hasan Sadikin Hospital Clinical Pathology Laboratory and MMP-9 levels were assessed together on February 15, 2015.

For statistical analysis, we do a normality test using the Saphiro-Wilks or Kolmogorov Smirnov test, followed by descriptive statistics and correlation test analysis between plasma MMP-9 levels and the degree of diastolic dysfunction using Pearson product-moment correlation analysis if data is normally distributed, or with Rank Spearman if the data is not normally distributed. Confounding variables that cannot be excluded will be analyzed through multivariate analysis.

This study has been approved by Dr. Hasan Sadikin Bandung hospital's Health Research Ethic Committee number LB.04.01/A05/EC/019/I/2015.

Results

Forty-six subjects met the inclusion criteria, and seven subjects were excluded with the following causes: 1 have incomplete data (no lateral E/e' data); 1 has CAD and DM; 4 have DM; 1 has CKD stage 3. The total number of research subjects was 39 people who were involved in the data processing.

In Table 1, there are 39 samples included in the study. The normality test done on numerical data was Shapiro-Wilk test because n ≤50. Normality tests show that the data on variables relative wall thickness, age, weight, height, and body mass index are normally distributed, whereas left ventricular mass, systolic blood pressure, and diastolic blood pressure were not normally distributed.

There are 14 male subjects in this study (35.9%) with 25 females (64.1%). The average age of the subjects was 55 (± 10) year, the average weight was 63.45 (±12.97) kg, mean height was 155.51 (±7.12) cm, mean body mass index 26.23 (± 5.08) kg/m^2, and average wall thickness was 0.7 (±0.15). Median systolic blood pressure was 140 (110-220) mmHg, median diastolic blood pressure was 80 (70-110) mmHg, and the median left ventricular mass index was 119.24 (103.05-205.69) g/m^2.

The median value of plasma MMP-9 levels in this study was 108 (4–460) ng/mL

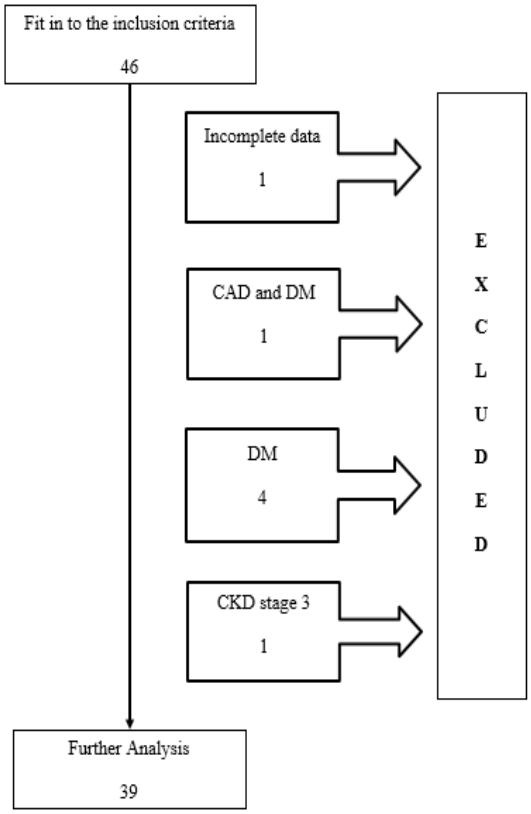

Fig. 1 Process Flow of Obtaining Research Samples

Table 1 Basic Characteristics of HHD Patients

Characteristics	Mean (±SD)	Median (min-max)	n (%) (n = 39)
Age (years)	55 (±10)		
Sex (male)			14 (35.9)
Weight (kg)	63.45 (±12.97)		
Height (cm)	155.51 (±7.12)		
Body mass index (kg/m^2)	26.23 (±5.08)		
Systolic blood pressure (mmHg)		140 (110–220)	
Diastolic blood pressure (mmHg)		80 (70–110)	
Left Ventricle mass index (g/m^2)		119.24 (103.05–205.69)	
Male		117.5 (115.03–146.9)	
Female		122.03 (103.05–205.69)	
Relative wall thickness	0.7 (±0.15)		
Left Ventricular Ejection Fraction	72.62 (±8.537)	73 (56–88)	

SD: Standard Deviation

Table 2 Median Value of Plasma MMP-9 and E/e'

Parameters	Median (min.-max.)
Plasma MMP-9 level (ng/mL)	108 (4–460)
E/e'	10,99 (6.2–20.42)

Table 3 Correlation between plasma MMP-9 level and E/e'

Parameter	Coefficient correlation (r)	P-value
MMP-9 — E/e'	0.416	0.004

Note: Correlation analysis uses Rank Spearman correlation analysis, significant if P<0.05

and the median value of E/e' was 10.99 (6.2-20.42) (Table 2).

The correlation analysis between plasma levels of MMP-9 and E/e' was shown in Table 3 and Fig. 2, presented in a scatter plot.

Based on the data elaborated above, we can conclude that the MMP-9 plasma level is moderate-positively correlated with E/e' parameter, with r value=0.416 and p=0.004 (<0.05).

Discussion

The median left ventricular mass index in this study was 119.24 (103.05-205.69) g/m^2, which is smaller than a similar study conducted by Ahmed *et al.*[15] (162±6 g/m^2), but greater than that of Tayebjee *et al*.[16] The difference between this study and those studies may be due to the differences of inclusion criteria and the criteria for left ventricular hypertrophy used. This study used left ventricular hypertrophy criteria based on ASE and EAE guidelines, which are 115 g/m^2 for males and 95 g/m^2 for females for left ventricular mass index.[10]

Plasma MMP-9 median level in this study was 108 (4–460) ng/mL. Other studies have had differing MMP-9 levels and these differences may occur due to differences in the testing technique used.

This study revealed MMP-9 plasma levels were positively correlated with E/e', which means that the higher the plasma levels of MMP-9, the higher the E/e' value. This concludes that MMP-9 plasma levels are positively correlated with diastolic dysfunction in concentric HHD patients.

The association of MMP-9 level with left ventricular function has been under extensive studies. MMP-9 level relationship with left ventricular systolic function in post-myocardial infarction patients and low ejection fraction-heart failure have been widely investigated, but few studies have looked at the association of MMP-9 with diastolic function.

In previous studies done on this topic, the relationship between MMP-9 plasma levels and diastolic function is still controversial.

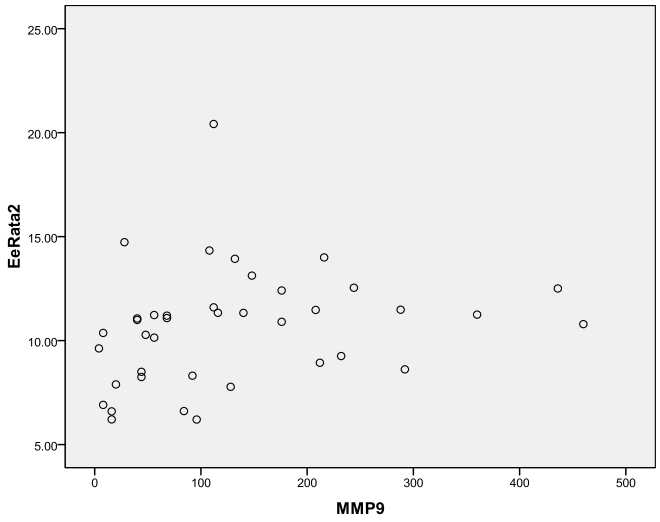

Fig. 2 Correlation between Plasma MMP-9 Levels and Diastolic Dysfunction as Measured by the E/e' test

This study result is supported by Ahmed *et al*.[15] and Martos *et al.*[17] studies, with the result of a significant relationship between MMP-9 levels and diastolic dysfunction. This study is not supported by the result of the study conducted by Tayebjee *et al.*[16] who stated that there was no significant relationship between MMP-9 levels and diastolic dysfunction.

The coefficient correlation (r) between MMP-9 and E/e' in Tayebjee, et al[16] was -0.115, which did not statistically significant (p=0.349). Unfortunately, studies conducted by Ahmed *et al.*[15] and Martos *et al*.[17] did not mention the coefficient correlation between MMP-9 and E/e'.

The difference of results in the study by Tayebjee *et al*.[16] and this study may be caused by the differences in the study population. The study of Tayebjee *et al.*[16] compared all hypertensive patients with or without left ventricular hypertrophy, whereas in this study, the population is patients with a more specific left ventricular hypertrophy, which is the concentric type of left ventricular hypertrophy.

A process that may explain the increase in plasma MMP-9 levels in patients with HHD with diastolic dysfunction is described by Martos et al[17]. Matrix Metalloproteinase-9 has collagen and extracellular matrix (ECM) turnover activity. Changes in cardiac ECM have an extensive role in terms of ventricular contraction function, both systolic and diastolic. High levels of MMP-9 cause a high turnover of collagen which is the main component of ECM. Among these collagens, there is elastin which functions to maintain the flexibility of the heart muscle. One of the activities of MMP-9 is to activate elastase which causes an increase in elastin degradation. The loss of elastin in the heart muscle and blood vessels causes stiffness of the heart and blood vessels that contribute to an increase in the degree of diastolic dysfunction. Matrix Metalloproteinase-9 also has a profibrotic effect, which means that the increasing levels of MMP-9 will increase the occurrence of fibrosis processes which will also increase the stiffness of the heart muscle and blood vessels, thus worsening the degree of diastolic dysfunction.[17]

The limitation of this study is that most of the exclusion criterias were obtained from the patient's history with only a small part of the study sample had the results of diagnostic examinations, thus allowing for information bias.

In conclusion, there is a moderate positive correlation between plasma MMP-9 levels and diastolic function abnormalities as measured by E/e' examination in concentric HHD patients. Further study is needed to compare the normal population and the population with diastolic dysfunction to determine the cut-off value of MMP-9 levels in diastolic dysfunction.

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Cardiovascular-Related Death Risk Factors in Hypertensive Patients: Indonesia Family Life Survey 2000–2014

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2185
IJIHS. 2021;9(1):25–29

Received:
October 27, 2020

Accepted:
March 30, 2021

Abstract

Objective: To determine the characteristics of the risk factors of cardiovascular death in hypertensive patients in Indonesia based on the Indonesian Family Life Survey (IFLS) longitudinal data.

Methods: This was a retrospective descriptive study on secondary data from the IFLS population starting from2000 and was followed up in 2007 and 2014. The inclusion criteria for participation were15 years old or older, had hypertension, had cardiovascular events as thecause of death, and had complete data in both IFLS 3 (2000) and IFLS 4 (2007).

Results: The IFLS 5 (2014) reported 918 deaths among eligible subjects with complete data, both in IFLS 3 (2000) and IFLS 4 (2007). Of those, a total of 608 subjects experienced hypertension started from 2000 and/or 2007. Of these deaths, 112 were due to cardiovascular events. Cardiovascular death was more common in males (58.9%), age of >65 years old when died (47.3%), had poor socioeconomic status (24.1%), and with normal body mass index (54.9%).

Conclusion: Male, late adulthood, low level of education, normal BMI, and poor socioeconomic status represented the greater risks of cardiovascular death among hypertensive patients in Indonesia.

Keywords: Cardiovascular death, hypertension, IFLS, risk factor

Introduction

Cardiovascular disease is the leading cause of death worldwide.[1, 2] There were 422,7 million cardiovascular cases and 17.92 million deaths in 2015.[2] Cardiovascular events in patients with hypertension are influenced by modifiable and non-modifiable risk factors.[3, 4] The global prevalence of hypertension is 1,13 billion in 2015.[5] The overall prevalence of hypertension in adults is estimated to be 30-45%, with higher proportion in males (24%) than females (20%).[5] Data from basic health research in 2018 showed the prevalence of hypertension in Indonesia was 34.1% (increased from 25.8% in 2013).[6]

Indonesia Family Life Survey is a large-scale series of cross-sectional study conducted by RAND Corporation in Indonesia.[7, 8] It has been conducted five times (1993, 1997, 2000, 2007, 2014) with re-contact rates higher compared to the similar survey in the United States and Europe.[7,8] The IFLS represented of 83% of the Indonesia population, provinces in west and central part of Indonesia were included. Individual and household factors such as age, gender, education, income, household composition, subjective and objective health measurements and biomarkers, health risk behaviors, healthcare utilisation, cognitive health, and subjective wellbeing were included in the IFLS. Thus, it can provide an opportunity to obtain secondary data on risk factors of cardiovascular death from hypertensive

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patients in Indonesia.[7, 8] This study aimed to determine the risk factors of cardiovascular death in hypertensive patients in Indonesia based on IFLS longitudinal data.[7, 8]

Methods

This was a retrospective descriptive study based on secondary data from IFLS 3 (2000), IFLS 4 (2007) and IFLS 5 (2014). The study population was all subjects who were reported died in IFLS 5. The inclusion criteria were age over 15 years old, had hypertension in 2000 and/or 2014 data, and death due to cardiovascular events. Subjects with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) were excluded from this study. T2DM and CKD were diagnosed through self reported. Data were extracted using STATACause of death were taken from IFLS 5 exit form file, blood pressure measurement report on IFLS 3 (hh00_all_dta, table bus1_1. dta) and IFLS 4 (hh07_all_dta, table bus1_1. dta) was calculated as average for systolic and diastolic blood pressure and defined as hypertension if systolic ≥140 and/or diastolic ≥90 mmhg were taken from (hh00_all_dta table us07,hh07_all_dta table us07 and hh14_ all_dta table us07), age of death were taken from (hh14_all_dta table fe1_1.dta), gender were taken from (hh00_all_dta table ar07, hh07_all_dta table ar07 and hh14_all_dta table ar07), education were taken from b3a_dl1.dta file, body mass index were taken from (hh00_ all_dta table bus_us.dta, hh07_all_dta table bus_us.dta, hh14_all_dta table bus_us.dta), assessment of socioeconomic status based on the quintile of asset ownership using the Principal Component Analysis (PCA) method were taken from table hrtype, measurement body mass index is calculating weight and height, were taken from bus_us.dta, cigarette smoking were taken from table b3b_km.

Blood pressure and BMI calculation of IFLS participants were measured by trained nurses. Blood pressure were measured using an Omron meter, HEM-7203, three times on alternate arms in a seated position.[8] The BMI was classified according to Asian criteria: normal (18.5 to <23.0 kg/m^2), overweight (23.0 to <25.0 kg/m^2), and obese (25+ kg/m^2). The smoking status was determined on the questionnaire response to 'Do you still have the habit or have you totally quit?'. The complete details of IFLS study design and methods have been described elsewhere.[7, 8] This study had received approval from the Research Ethics Committee Dr. Hasan Sadikin General Hospital Bandung No. LB.02.01/X.6.5/77/2020.

Results

There are 918 subjects reported as died in IFLS 5 (2014) which can be tracked back to data in IFLS 3 (2000) and IFLS 4 (2007), leaving a total of 608 subjects with hypertension in the data of year 2000 and 2007, and only 112 died.

Among 112 subjects who died due to cardiovascular events with the history of hypertension, most of them were males (58.9%) aged >65 years old (47.3%), Elementary school graduates (49,1%), poor socioeconomic status (24.1%), non-smoker (67%), and normal BMI (54.9%; Table)

Cardiovascular death in both gender was more common in primary school graduates. In males (31.3%) and females (17.9%; Fig. 1).

Cardiovascular death in both gender was more common in the age of >65 years old (Fig. 2).

Table Subjects Characteristic

Variables	n (%)
Sex	
Male	66 (58,9)
Level of Education	
No School	30 (26,8)
Elementary school	55 (49,1)
Junior high school	9 (8,0)
Senior high school	16 (14,3)
University	2 (1,8)
Age of death	
25 to 45	5 (4,5)
46 to 55	23 (20,5)
56 to 65	31 (27,7)
>65	53 (47,3)
Socioeconomic status	
Very poor	24 (21,4)
Poor	27 (24,1)
Middle	25 (22,3)
High	21 (18,8)
Very high	15 (13,4)
Cigarette Smoking	
Yes	37 (33,0)
No	75 (67,0)
BMI*	**n=102**
Underweight	10 (9,8)
Normal	56 (54,9)
Overweight	26 (25,5)
Obese	10 (9,8)

*Data not complete; BMI=Body mass index

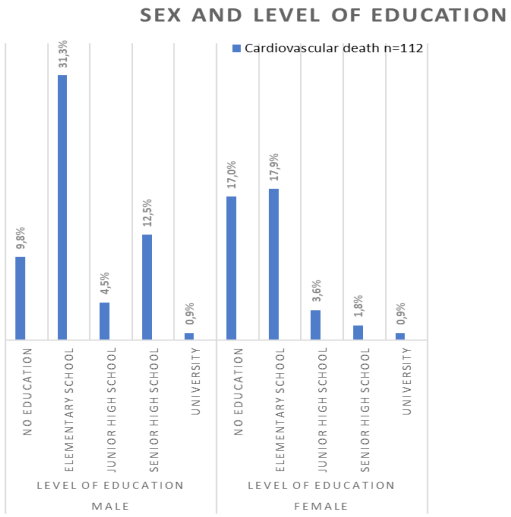

Fig 1. Sex and Level of Education Distribution

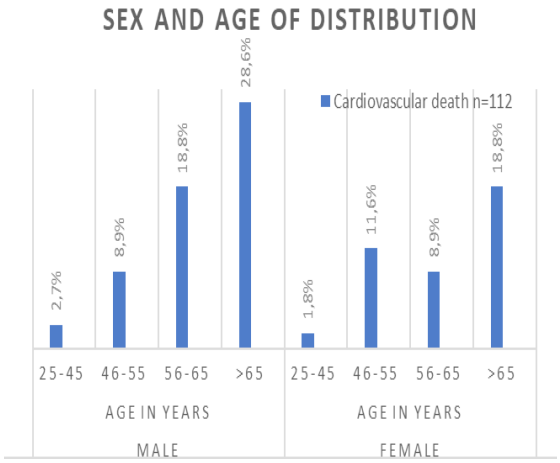

Fig 2. Sex and Age Distribution

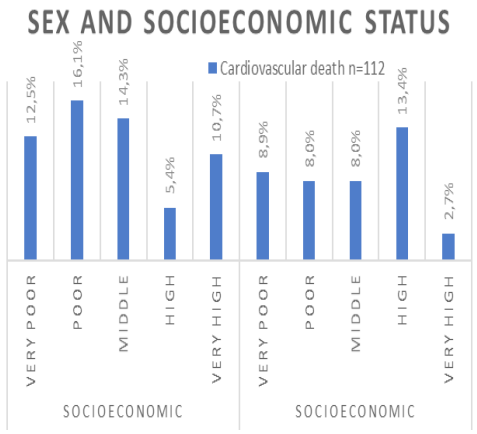

Fig 3. Sex and Socioeconomic Status

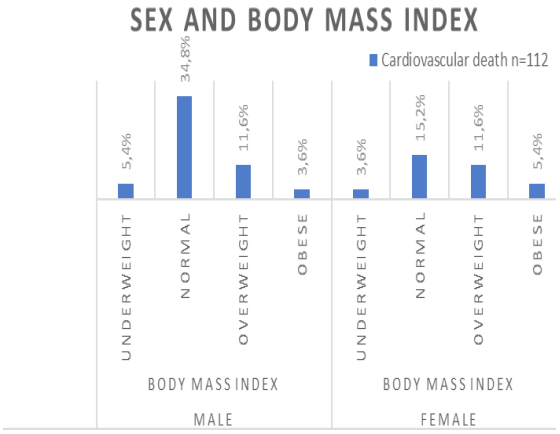

Fig 4. Sex and BMI distribution

Cardiovascular death in males was more common in poor income (16.1%). In females, cardiovascular death was more common in high income (13.4%; Fig. 3).

Cardiovascular death in both gender was more common in normal BMI, In males 34,8% and females 15,2%. The distribution of BMI status amongst gender were shown in Fig. 4.

Discussion

This study found that males had a higher distribution of cardiovascular death compared to females. These results are consistent with data from the European Society of Cardiology (ESC), and the American Heart Association (AHA) that stated a male had a higher risk of cardiovascular disease compared to females.[4,5] A study conducted based on Indonesia Basic Health Research 2013 by Ghani *et al* [9] stated that women had 1.22 times greater risk of coronary heart disease.There is an increase in number of death in patients aged over 46 years old with the highest rate in subjects >65 years old. This result is similar to those obtained by Ghani et al. in 2016, which found that the risk of stroke increased with age, and patients aged >55 years old had 10.23 times higher risk compared to those aged 15–44 years old.[10] There is an increase in the cardiovascular

death profile and atherosclerotic process in males as age increases.[11] While females of childbearing age have a high level of estrogen, which can protect against cardiovascular risk factors, the risk of cardiovascular disease increases two to fourfold after menopause.[11, 12] Men were more likely to have heavy plaques associated with impaired blood flow. This plaque has characteristics of thin and rich in fat or necrotic nuclei that are rich in lipids and have a high risk of cardiovascular death.[13] In addition, endothelial dysfunction and arterial stiffness are more common in men than women in the age spectrum up to the sixth decade. Before menopause, women are relatively protected from cardiovascular disease. In menopausal women, the risk of cardiovascular disease increases. This is related to a decrease in sex hormones that have been shown to play an important role in cardiovascular disease development at the onset of older age.[12]

This study showed that deaths due to cardiovascular events are more common in poor education level. In addition, poor education level subjects have limited access to health services. These results are consistent with a study conducted by Ghani et al. that identified dominant risk factors for stroke based on Indonesia Basic Health Research 2013. Ghani *et al.*[9] found that stroke was more common in poor education. This is due to lack of knowledge related to the impact of bad lifestyle behavior such as high-fat diet which will lead to degenerative disease.[10]

Another study based on IFLS conducted by Gumilang et. showed hypertension incidence was lower in subjects who attended school (17.3%) compared to subjects who didn't attend school. There was a decrease in incidence as subjects had higher education.[14] In addition, a study conducted by Chiara et al. showed that level of education were independently associated with increased cardiovascular risk factors globally.[15]

Cardiovascular death is more frequent in poor socioeconomic subjects. Other study based on IFLS 2007 and 2017 conducted by Sudharsanan et al. showed that duration of socioeconomic status and cardiovascular risk factors (obesity, hypertension, and cigarette smoking) play an important role in the association between individual characteristics and mortality.[16]

Cardiovascular death among hypertensive patients was more prevalent in non-smokers. While this finding seemed contrary with the current evidence, there were several concerns with the result. Firstly, our data only showed current smoking status. We did not define the duration, quantity of cigarrete smoking, and history of previous smoking which could affected the result of our findings. Secondly, we did not know whether the non-smokers had more comorbidities that we did not include in the studies, such as dyslipidemia, history of premature vascular disease, history of cerebrovascular disease.

More subjects who died due to cardiovascular disease having normal body mass index (54,9%), while the lowest was underweight (9.8%). Data from ESC and AHA showed that people with higher BMI are at risk of having cardiovascular disease.[4, 5] A study based on IFLS 5 conducted by Kasyani et al. showed that there was a significant association between nutritional status with hypertension, higher BMI will increase the risk of developing hypertension.[19] Ghani et al. stated low body mass index has a risk of coronary heart disease 1.31 times for the incidence of coronary heart disease.[4, 5, 13] Until lately, metabolically healthy obesity (MHO) has drawn increasing attention and has been reported to have better outcome than the obesity with metabolic abnormalities.[20] The definition of MHO is not uniform, but it is commonly described as obesity without or less than two of the five metabolic abnormalities (high plasma triglyceride concentration, high fasting blood glucose, low high-density lipoprotein cholesterol concentration, and large waist circumference, and high blood pressure).[20] In this study, we did not include any other parameters of metabolic dysfunction other than hypertension, therefore we did not know whether the overweight and obesity group had any other metabolic abnormalities. Furthermore, we did not know whether the hypertensive population were using any anti-hypertensive drugs and whether the blood pressure was under control. These factors might largely affected the result of the study.

Some limitations should be noted. The data collections were separated by 7 years, many subjects from previous survey were not contactable on the following surveys; smoking history, and passive smoking status were also limited. Moreover, the descriptive nature of the study design without including numerous cardiovascular risk factors in the baseline characteristics sample should be taken into account as major limitations of this study. Further analytical study with multivariate analysis might be necessary to confirm any findings from this study. It is concluded that cardiovascular death among hypertensive

patients in Indonesia is more prevalent in male, late adulthood, low level of education, normal BMI, and poor socioeconomic status.

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Effects of Low-level Laser Therapy on Fibroblast Density in Achilles Tendon Rupture Healing

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2232
IJIHS. 2021;9(1):13–18

Received:
December 11, 2020

Accepted:
March 30, 2021

Abstract

Objective: To investigate the effect of low-level laser therapy (LLLT) on fibroblast proliferation as a part of the tendon healing cascade.

Methods: This was an unpaired comparative experimental animal laboratory study with one control groups and two experimental groups, each consisted of 10 Sprague Dawley rats. The experimental groups 1 and 2 were given infrared irradiation for 15 minutes and 30 minutes per day, respectively, after having their achilles tendon partially cut. Histological assessment was carried out to assess the fibroblast density in healing site after three weeks on intervention.

Results: The median values of fibroblast density in group 1, group 2, and control group were 1, 2, and 1, respectively, with a p-value of 0.014. No significant difference (p=0.123) was identified on Mann-Whitney test between the fibroblast density of group 1 and group 2. The same was also true forgroup 1 and control group (p=0.315). A significant difference was found between group 2 and control group (p=0.005).

Conclusions: A regime of LLLT irradiation of 30 min/day for two weeks (1080 J cm-2) improves the fibroblast proliferation amidst tendon healing in a partially injured achilles tendon in a rat model, which is not seen in the regime with a 15 min/day duration. This emphasizes the significance of irradiation time to improve tendon healing, despite the deficient understanding of the mechanism.

Keywords: Achilles, fibroblast, laser, rupture

Introduction

Achilles tendon injuries are common in athletes, due to high stress with jumping and landing, or by overuse. The overall incidence of Achilles tendon rupture is on the rise recently. Nevertheless, controversy has surrounded the optimal treatment of acute Achilles tendon rupture.[1] Nonoperative treatment as an alternative to operative treatment, is a cost-effective option and could be especially suitable for the general population that is not that active.[2,3] In 2005, Ingvar, Tagil, and Eneroth had reported 7% re-rupture rate of 198 consecutive Achilles tendon rupture patients which treated nonoperatively.[4] Thus, surgical intervention as a primary treatment became questionable when taking cost and surgical complications into consideration, such as infection, pain, adhesion, and post-operative scarring.

One of the therapeutic modalities that can be done to enhance the healing of musculoskeletal injuries including tendon rupture is low-level laser therapy (LLLT) such as infrared therapy. LLLT is a general

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term describing a treatment method based on photobiomodulation principles, that induce a biological effects on organisms, due to the interactions of photons with molecules in the cells or tissues. This process is referred to as "low-level" because its low energy compared to other form of laser therapy such as ablation, cutting, or coagulation. LLLT triggers the release of nitric oxide (NO), a small endogenous molecule with many physiological effects on the body systems.[5] Bokhari and Murrell stated that in animal models, competitive inhibition of nitric oxide synthases (NOS) resulted in reduced tendon healing, whereas the addition of NO resulted in enhanced tendon healing.[6]

The results of research and clinical investigations into the effects of infrared, among others, show a potentially effective clinical outcome and a low risk.[7,8] Joensen *et al*. had reported a significant differences in tendon thickness in rats which received LLLT when compared to placebo group.[9] In one study, low-level laser irradiation applied to a cell culture was also known to increase fibroblast cell proliferation and reduces cell death in a dose-dependent manner. In patients, LLLT promotes tendon healing, alleviates the pain, and assists flexibility of soft tissue and joints, thus serves as a proper adjuvant therapy in tendon repair.[11] The applications of LLLT, in contrast with the past-well established terminology linked to the use of lasers, is now performed with a wide variety of different light sources, such as LEDs and lamps.

Although scientific data in relation to infrared application are increasing, the understanding of its effect to injured tendon healing in cellular level is still limited. LLLT remains somewhat controversial for two principle reasons. First, there are uncertainties about the fundamental molecular and cellular mechanisms responsible for signals transduction. Second, there are significant variations in terms of dosimetry parameters: wavelength, irradiance or power density, pulse structure, coherence, polarization, energy, fluence, irradiation time, contact vs non-contact application, and repetition regiment.[12]

It is important to assess the optimal dose of light for any specific use. The aim of this study was to investigate effects of infrared interaction in different dose to the tendon fibroblast proliferation shown histologically.

Methods

This research was an experimental study with simple random sampling. We divided the animals into three groups, specifically one control group and two experimental animal groups, getting infrared irradiation for 15 minutes (group 1) and 30 minutes (group 2), respectively. The dependent variables in this research was histologically analyzed fibroblast density. This study was approved in advance by Health Research Ethics Committee of Universitas Padjadjaran No. 120/UN6.KEP/EC/2020 (Reg No. 0319121706).

The study animals comprised of 30 male Sprague Dawley rats from Animal Laboratory of Universitas Padjadjaran Medical School, weighing 250-300 g, which had their Achilles tendon partially cut and divided into three groups. Rats were kept at bioterium for one week, placed in a quiet room with adequate lighting and temperature maintained at 20°-25°C, with food and water *ad libitum*.

The experimental procedure was carried out in four steps. First, all animals were anesthetized using 0.5 ml intramuscular ketamine, carried out cleaning and hair removal in the heel area. A longitudinal skin and subcutaneous incision was performed on the posteromedial side of the heel with attention to antiseptic procedure. Deepened incision until the Achilles tendon was done followed by a sharp hemisection to the Achiles tendon with a scalpel blade size no. 15, at 0.5 cm above its insertion to the calcaneus bone (Fig. 1a). The surgical wound was closed layer by layer using polypropylene thread size 4-0 and standard dressing. The limbs were not immobilized due its partial cut design. Other consideration was to prevent inhibition of radiation by the enclosing cast or splint. Second step, animals in experimental group were irradiated starting at 5th day after treatment using a Philips Infraphil 13379F/479, 150W lamp, ranging from 600 to 1500 nm, with a peak at 1000 nm, at a 30 cm distance from the animals. Animals had their affected leg irradiated while fixed on a board. The other body areas were covered with a wet towel. The duration was differed between two experimental groups, specifically 15 min (540 J cm^{-2}) and 30 minutes (1080 J cm^{-2}) a day for fourteen days. To prevent infrared heating, the temperature was controlled by indoors air-conditioning with plenty of ventilation and routine temperature measurement using thermometer (Fig. 1b).

Three weeks after initial treatment, the animals were killed by injection of 1 ml saturated potassium chloride solution to cause cardiac arrest. The tissue around the hemisected tendon were taken parallel to the joint ends *en bloc*, and then fixed in 10%

formaldehyde solution. Tendon specimens were taken and examined histologically under haematoxylin-eosin staining, particularly at hemisection site (Fig. 2). Fibroblast density was evaluated semi-quantitatively using three scales (0: absent, 1: mild appearance, and 2: marked appearance) and recorded for comparison between groups (Fig. 3). Histological analysis was conducted by an independent histopathological expert.

Data analysis was performed using Statistics Social Service Program (SPSS) ver. 25 for Windows (SPSS Inc. Chicago, IL, USA). Descriptive analysis was carried out and data distribution and normality tests were performed to determine whether parametric or nonparametric analysis was used, and comparative hypothesis testing of numerical variables was carried out using One Way ANOVA for parametric testing or Kruskal Wallis test for nonparametric tests.

Results

Table 1 shows the distribution of fibroblast density among three groups. Score maximum of 2 were found in both experimental groups, but not in control group.

Kruskal Wallis statistical test followed by median test was used for analysis because the data were ordinal, abnormally distributed with a significance of 5%. Calculated p value was 0.014, which means that there was a significant difference in the value median fibroblast density between the three groups.

It can be seen that the fibroblast density has the highest median in the experimental group 2. Considering there was a significant difference between groups, a further test was carried out with the median test to compare between the two groups (Table 2). There was no significance difference between fibroblast density between experimental group 1 and group 2, as well as between experimental group 1 and control group ($p>0.05$). Rather, the difference of medians between experimental group and control group was significant ($p=0.005$).

Table 2 Median Test Results for Fibroblast Density Variable

Group Comparison	p value
Experimental Group 1 and Group 2	0.355
Experimental Group 1 and Control Group	0.778
Experimental Group 2 and Control Group	0.005

Discussion

The results of this study were in a concordance with prior basic studies stating that infrared therapy in tissue healing can increase fibroblast proliferation.[10,15] Additional value of this study to the LLLT application is the distinction made by dosage differences, specifically the irradiation time. This study showed histologically an increase of fibroblast cell density following a LLLT. Notable findings here was the different results among experimental groups, thus emphasizing the importance of the dosage setting, specifically different irradiation time of similar energy. In this study, irradiation of 540 J cm^{-2} for two weeks yielded insignificant result difference with control group.

Low-level laser therapy (LLLT) refers to the use of photons at a non-thermal irradiance to alter biological activity. The main medical applications of LLLT are reducing pain and inflammation, augmenting tissue repair, promoting regeneration of different tissues, and preventing tissue damage in situations where it is likely to occur.[12,13] Avci *et al.*[12] has also mentioned that this procedure is referred to as 'low-level' because the energy or power densities employed are low compared to other forms of laser therapy such as ablation, cutting, and thermal tissue coagulation. It can be implied that the effects of irradiation are a response to the light and not due to heat.[14]

The increase in the number of fibroblasts mediates the production of collagen. Infrared can also increase the activity of macrophages in the phagocytic process, secretion of growth

Table 1 Fibroblast Density According to Groups

Groups	N	Min.	Max.	Median	Mean	SD	p-value
Experimental Group 1	10	0	2	1	1.00	0.816	0.014
Experimental Group 2	10	0	2	2	1.60	0.699	
Control group	10	0	1	1	0.60	0.516	

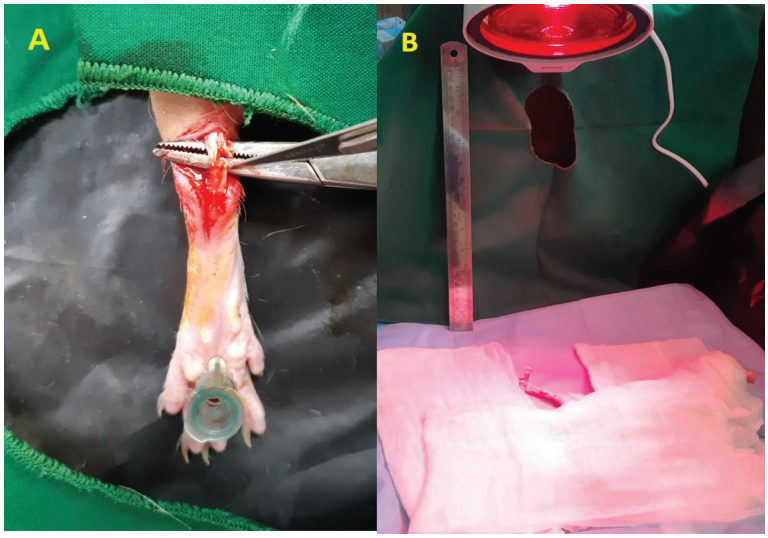

Fig. 1 (A) Partial Achilles Tendon Cutting in the Rat; (B) LLLT Irradiation Set-Up

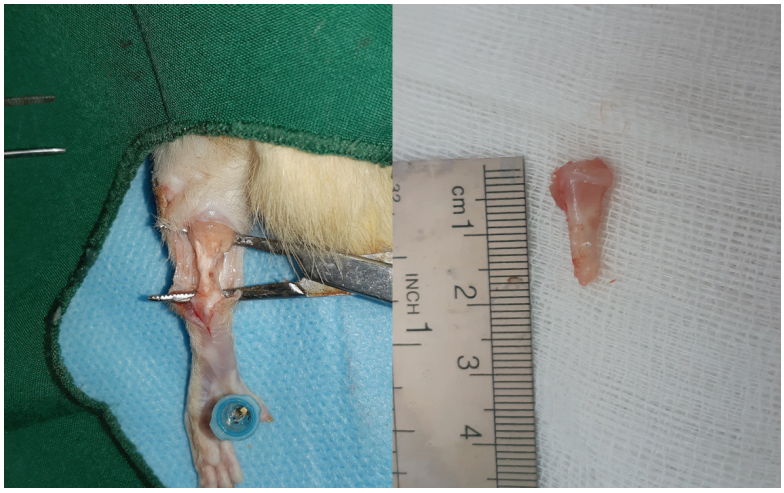

Fig. 2 Macroscopic Finding of Healed Achilles Tendon

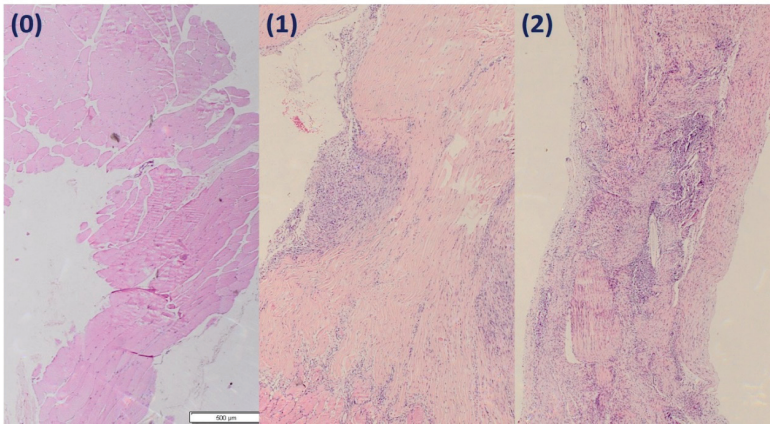

Fig. 3 Histological Findings Showing the Different Result of Fibroblast Density, Specifically Scored as 0 (absent), 1 (mild), and 2 (marked)

factors, and stimulate collagen synthesis. In addition, it can also stimulate the formation of neovascularization, which will support increased perfusion and oxygenation, as well as regeneration of endothelial cells. Fibroblasts are cells that have a significant role in the tendon healing process. Fibroblasts secrete essential substances and collagen, which form scar tissue as a substitute for defects in wounds. The fibroblast proliferation process uses fibrin threads originating from the blood clotting process as a framework, and then the fibrin disappears according to collagen deposition.[16]

Infrared therapy has been shown to stimulate nitric oxide production. Nitric oxide is a small endogenous molecule with multiple effects on the body's systems. Nitric oxide is involved in a wide range of biological functions in the body, including vasodilation, immune response, and neurotransmission as reported by Wink *et al*.[17] The fact is that infrared can penetrate deep into wound tissue and allow non-invasive treatment of the wound healing process. The visible, infrared waves are easily absorbed by the surface components of the blood and muscle surfaces, limiting the penetration of the tissue to <10 mm. Shortwave infrared (810 nm) is not easily absorbed and has a much greater depth of tissue penetration of 30-40 mm or more and thus provides more significant deposition of photons at the site of injury.[18]

The effect of providing heat to the body via infrared can also increase collagen fibers in the tendons and joint capsules, reduce the viscosity of the fluid tissue elements, reduce joint stiffness, reduce muscle spasm, vasodilate blood vessels, and increase metabolism. Some of the positive clinical effects of infrared has been introduced, including those for reducing rheumatic knee pain, as well as its impact on wound healing.[19]

There are some limitations of this study. To date, no proper method for measuring the parameters of the biological effects of LLLT, including the effective wavelength, irradiation time, and intensity has been developed. Tsai and Hamblin correctly noted that if certain parameters such as irradiation type, laser wavelength, continuous vs pulsed irradiation, pulse shape, and target area are changed, it may not be possible to compare between studies.[14] Thus, it is difficult to compare fairly between many LLLT modalities for its efficacy as shown by many studies. However, Hsu *et al.*[20] had reported the effective irradiation time as an important factor for the biological application of LLLT. Among different irradiation times, specifically 15, 30, 45, and 60 minutes, the far-infrared biological index of 30 minutes irradiation was significantly higher than those of the other durations.There was a potential bias of this study as well, resulting of a single observer analysing the histological specimens. However, this study may provide the framework to define the guidelines for LLLT therapy regarding Achilles tendon rupture.

Other problematics included disadvantages of adjusting this study for clinical relevance in human, concerning the age and dosage adaptation. This short-term study was also unable to identify the side effects in rats, both locally and systemically.

In conclusion, low-level laser irradiation at 1080 J cm^{-2} per day, administered for fourteen days appeared to increase the fibroblast density of injured Achilles tendon in rat models, compared with control group and experimental group receiving 540 J cm^{-2}. This experiment is useful for investigating the positive effects of low-level laser therapy to enhance tendon healing and optimal duration of therapy. However, considering the healing cascade, we believe this results is only applicable for acute healing phase. Further studies using this model should explore the maximum duration allowed to avoid harmful effects such as tissue damage.

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Association between Malnutrition Inflammation Score and Latent Tuberculosis among Chronic Hemodialysis Patients

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2370
IJIHS. 2021;9(1):19–24

Received:
February 24, 2021

Accepted:
March 30, 2021

Abstract

Objective: To investigate the association of malnutrition with latent tuberculosis (TB) among chronic kidney disease (CKD) patients on hemodialysis (HD).

Methods: This was a cross-sectional study conducted at the Hemodiaylisis Unit of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Subjects were patients aged >18 years who had undergone HD twice a week for at least three months. Patients suspected of active tuberculosis (TB), malignancy, or immunocompromised were excluded. Latent TB was diagnosed using the interferon-gamma release assays (IGRA). Malnutrition was defined by a malnutrition inflammation score (MIS) of less than 5. All data including age, sex, CKD etiologies, and laboratory findings were obtained and recorded in a case report form.

Results: A total of 120 subjects were involved in this study. Subjects with positive, negative, and indeterminate IGRA results were 39.2%, 56.7%, and 4.2%, respectively. There was no significant differences in subjects characteristics between positive and negative IGRA subjects. The MIS>5 was shown to have no statistically significant association with positive IGRA subjects (OR=3.47, 95%CI 0.93–12.93).

Conclusion: Malnutrition based on an MIS score of less than 5 is not statically associated, but clinically associated, with latent TB. Further causal inference study to investigate these associations is needed.

Keywords: Chronic kidney disease, hemodialysis, latent tuberculosis, malnutrition

Introduction

Chronic kidney disease (CKD) patients have a greater risk of tuberculosis (TBC) compared to normal kidney function population. Suggestively, uremic retention in CKD patient alters immune response through various mechanisms. Declined phagocytosis function of granulocytes and monocytes/macrophages, suboptimal capacity of antigen presentation by antigen presenting cells (APCs), decreased B lymphocytes production ability, decreased CD4+ and CD8+ T lymphocytes due to increased T lymphocytes apoptosis, and disturbed cell-mediated immunity are the implication of chronic uremic retention.[1]

Protein energy wasting (PEW) and its consequences are commonly occurred among CKD patients, particularly in patients on chronic haemodialysis (HD). Malnutrition also contributes to declined various physiologic functions. Estimating prevalence of PEW in CKD on HD patients is 18–75%.[2] *Malnutrition inflammation score* (MIS) is one of the quantitative nutrition assessment tools. It consists of medical history, physical examination, anthropometry, and laboratory parameters such as albumin, transferrin, total iron binding capacity (TIBC). Previous studies

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proposed MIS as risk stratification among CKD on HD patients in Asia. Five-years study to 809 chronic HD outpatients in South California investigated the association between MIS and health-related quality of life (Hr-QoL). Increased MIS (>2) is associated with double risk of mortality. Another study investigated 155 CKD on HD patients, and concluded that MIS ≥5 is considered as malnutrition.[3,4]muscle wasting and cachexia are common and strongly associated with mortality in CKD, which is reviewed here. RECENT FINDINGS: The malnutrition-inflammation score (KALANTAR Score

Malnutrition has strength relationship with TBC infection. Malnutrition on TBC infection decreases immunity secondary to lymphocyte production and immune cells proliferation. As a consequence, it aggravates the growth of mycobacteria and increases dissemination risk. Reactivation of latent or previous subclinical TBC infection is associated with nutrition status worsening.[5,6]as defined by low body mass index (BMI Moreover, low protein intake is also observed in latent TBC on CKD patients.[7]

Latent TBC infection is frequently not proper documented in CKD on HD patients. Ironically, CKD on HD patient is the one of high-risk population to develop TBC infection. A reported TBC prevalence among CKD on HD patients is 10.6%.[8] In patient with chronic dialysis, the risk of TBC reactivation is increases 10–25 times. Based on interferon-gamma release assay (IGRA), latent TBC is occurred in 22,2% among CKD on HD patients.

Malnutrition status on CKD patient can affect the immune response. It can increase risk of the developing active TBC from the latent one. Furthermore, investigation about association between MIS and latent TBC is needed. By understanding its, progressivity latent-to-active TBC can be monitored. It makes the management of CKD on HD patient more comprehensive, and be able to decreases morbidity and mortality, as well as HrQoL. Our study is aimed to investigate the association of MIS with latent tuberculosis on chronic HD patients.

Methods

This was an analytic-observational study with cross-sectional approach. This study is conducted on routine HD patients in Hemodialysis Unit of Dr. Hasan Sadikin General Hospital Bandung, with the subjects recruitment period of March–May 2020. Subjects aged >18 years and at least three-months with twice a week of HD were included in this study. Patients with malignancy history, infected by human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), getting immunosuppressive therapy, have TB history, or receiving anti-tuberculosis drugs were excluded from this study.

MIS have ten components including change in end-dialysis dry weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, decreased fat stores or loss of subcutaneous fat, muscle wasting, body mass index (BMI), serum albumin, and total iron binding capacity (TIBC). Each component has 0–3 severity score, hence MIS have 0–30 score in range.[9]we matched 203 ND-CKD and 203 TX patients from two independently assembled cohorts of patients based on estimated glomerular filtration rate (eGFR Malnutrition was defined as MIS greater than 5.[4]73% of HD and 71% of PD patients exhibited moderate malnutrition, whilst using MIS, 88% and 90%, respectively were malnourished. DMS and MIS correlated significantly in HD ($r2=0.552$, $p<0.001$

Latent TB was diagnosed according to IGRA results (QUANTIFERON-TB IGRA). IGRA test has been done in 24–48 hours and can be interpreted based on interferon gamma qualitatively according to Table 1.[10]

Subjects that fulfil inclusion criteria and not meet the exclusion criteria was examined by the assessor including history taking, physical examination, and laboratory examination. TB symptoms and sign is consisted of fever, dyspnea, decreased body weight, chronic diarrhea, and lymph node enlargement. All patients were examined for thorax x-ray that expertized by independent radiologist. By certain indications, acid fast bacilli (AFB) staining, AFB culture, abdominal ultrasound, and histopathological examination for lymph node enlargement. All asymptomatic patients were examined for IGRA before HD procedure.

All data were analyzed using SPSS 25.0. Data were managed using REDCap electronical data recorder. Categorical descriptive such as prevalence was analyzed using binomial exact test to reveal its 95% confidence interval. Unpaired T-test with Mann-Whitney as alternative was used for numerical comparison for two-groups. Each p value <0.05 was considered as statistically significant.

This study was conducted and ethically approved by Health Research Ethics Committee of Medical Research, Dr.Hasan Sadikin General Hospital. This study is a part of study project of

Tuberculosis on Chronic Kidney Disease (CKD) on Routine Hemodialysis in Dr. Hasan Sadikin General Hospital Bandung and Habibie Kidney Hospital, Bandung with Ethical Clearance Number of LB.02.01/X6.5/302/2019.

Results

A total of 120 subjects were involved in this study. Subjects with positive, negative, and indeterminate IGRA results were 39.2%, 56.7%, and 4.2%, respectively. Due to small number indeterminate IGRA results (5 subjects), we did not perform further analysis for indeterminate IGRA subjects. Hypertension was predominant as cause of CKD. There was no significant difference in sex distribution, mean of age, hemodialysis duration, hemoglobin levels, serum iron, transferrin saturation, TIBC, and serum albumin between positive and negative IGRA subjects ($p>0.05$). Etiologies of CKD, such as hypertension, diabetes mellitus, etc, were also not significantly different between positive and negative IGRA subjects ($p>0.05$). Detailed baseline characteristics of the subjects was described in Table 2.

According to bivariate analysis in Table 3, malnutrition (MIS>5) was more prevalent in positive IGRA subjects compared to negative IGRA subjects (93.6% vs 80.9%), but not statistically significant ($p=0.052$). MIS>5 was not significantly associated with positive IGRA results (OR=3.47, 95%CI 0.93–12.93).

Discussion

According to our results, the prevalence of latent TB among routine HD patients was 40.9%. This results is higher than two studies reported prevalence in Taiwan, as high-prevalence CKD country.[11,12] Another study in Korea has similar prevalence of positive IGRA results. Forty-two percent of patients who underwent kidney transplantation has positive IGRA results.[13] A study in India also reported the prevalence of latent TB among CKD on HD patients was 36%.[14] These facts are the evidence of latent TB is common in CKD on HD patients.

In our study, among 5 indeterminate IGRA subjects, two subjects has nill value more than 8, meanwhile the others have low mitogen value. This pattern can be occurred due to inadequate lymphocyte amount, decreased lymphocytes activities, IFN-inability of lymphocytes to produce IFN-γ, as well as inappropriate specimen handling.[10] In our study, among 5 indeterminate IGRA subjects, two subjects has nill value more than 8, meanwhile the others have low mitogen value. This pattern can be occurred due to inadequate lymphocyte amount, decreased lymphocytes activities, IFN-inability of lymphocytes to produce IFN-γ, as well as inappropriate specimen handling. On the other hand, indeterminate IGRA results also can be occurred suboptimal immune response to mitogen control or excessive baseline immune activity of the subjects (high nill value). Sharninghausen *et al.*[15] reported the indeterminate results occurred in 3.8% of their subjects, and is associated with low mitogen levels and high nill. Furthermore, Asian ethic, anemia, and hypoalbuminemia are the independent risk factors. Genetic polymorphism on the T cells and natural killer (NK) cells are also related with mitogen control. Phytogemagglutinin is also associated with genetic loci that causing alteration of the lymphocytes activity.

On latent TB infection, host immunity and mycobacteria virulence reach equilibrium state. Hence, it does not yield inflammation state that have effects on symptoms, body composition and size alteration, fat stores, muscle mass, and laboratory findings that

Table 1 Interpretation of QuantiFERON-TB IGRA

Interpretation	Nill	TB response	Mitogen Response
Positive	≤8.0	≥0.35 IU/ml and ≥25% of nill	Any
Negative	≤8.0	<0.35 IU/ml and <25% of nill	≥0.5
Indeterminate	≤8.0	<0.35 IU/ml and <25% of nill	<0.5
	≥8.0	Any	Any

Table 2 Subjects Characteristics

Subjects Characteristics	Total n=115	IGRA (+) n=47	IGRA (-) n=68	P value
Age (years)				
Mean ± SD	47±13	48±12	47±14	0.669[a]
Sex				
Male	54 (47.0)	26 (55.3)	28 (41.2)	0.135[c]
Female	61 (53.0)	21 (44.7)	40 (58.8)	
Hemodialysis duration				
Median (IQR)	50 (27–83)	45 (26–80)	52 (28–87)	0.527[b]
Etiology of CKD				
Hypertensive kidney disease	60 (52.2)	26 (55.3)	34 (50.0)	0.619[c]
Diabetic nephropathy	18 (15.7)	9 (19.1)	9 (13.2)	
Uric acid nephropathy	4 (3.5)	2 (4.3)	2 (2.9)	
Lupus nephropathy	2 (1.7)	1 (2.1)	1 (1.5)	
Obstructive nephropathy	1 (0.9)	1 (2.1)	0 (0.0)	
Glomerulopathy	23 (20.0)	6 (12.8)	17 (25.0)	
Chronic pyelonephritis	6 (5.2)	2 (4.3)	4 (5.9)	
Polycystic kidney diseases	1 (1.5)	0 (0.0)	1 (1.5)	
Laboratory				
Hemoglobin (g/dL)				
Median (IQR)	9.3 (8.2–10.3)	9.4 (8.4 –9.7)	9.3 (8.2–10.3)	0.639[b]
Serum Iron (ug/dL)				
Median (IQR)	50 (41–72)	48 (41–72)	51 (41–72)	0.842[b]
Transferrin saturation (%)				
Median (IQR)	25.3 (19.9 – 37.8)	25.9 (20.4 – 37.3)	24.5 (19.3–37.3)	0.585[b]
Ferritin (ng/mL)				
Median (IQR)	412.6 (166.6–780.3)	397.8 (139.0–704.9)	427.9 (245.2–963.9)	0.270[b]
TIBC (mg/dL)				
Median (IQR)	201 (174–242)	190 (166–246)	204 (178–237)	0.400[b]
Albumin (g/dL)				
Median (IQR)	3.36 (3.17–3.54)	3.35 (3.20–3.46)	3.36 (3.17–3.57)	0.680[b]

Test used: [a]*Unpaired t-test* [b]*Mann Whitney,* [c]*Chi Square,* [d]*Fisher Exact*

Table 3 Association of Latent TB based on IGRA and Malnutrition based on MIS

MIS categories	IGRA (+) n=47	IGRA (-) n=68	P value	OR (95% CI)
>5	44 (93.6)	55 (80.9)	0.052	3.47(0.93 – 12.93)
≤5	3 (6.4)	13 (19.1)		

[a]Analyzed by *Chi Square;* IGRA: interferon-gamma release assay

associated with inflammation. Accordingly, in latent TB infection, mycobacteria proliferation is controlled. It is indicated by efficient cellular interaction and granuloma formation to prevent mycobacteria dissemination.[16] Latent phase of TB infection represents equilibrium state, when host immunity capable to control the infection, but not fully eradicate the pathogens. Granuloma represents immunological and physical barrier to suppress the infection and prevent the dissemination. They play dynamic and sustainable immune control to the mycobacteria replication. Latent TB patients are the highest reservoir for transmission potential. Although majority of patients are not death due to tuberculosis, the highest hazard are TB reactivation and close contact transmission. Estimated risk for TB reactivation is 10%. Disrupted immunity, such as HIV infection, increases the risk up to 10% per year.[6]

This study reveals no significant difference of MIS between positive and negative IGRA results. Suggestively, it is caused by subjective component in MIS assessment such as medical history. MIS have several subjective components such as daily nutritional intake and gastrointestinal symptoms. Depression, fatigue, and cognitive alteration are commonly occurred on CKD on HD patients. Hence, the assessment can be biased. However, MIS is still comparable with dialysis malnutrition score, and strongly correlated with other objective malnutrition parameters including BMI, triceps skin folds, mid-arm muscle area, mid-arm muscle circumference, and serum albumin.[17]one of the strongest predictors of morbidity and mortality in maintenance haemodialysis (HD Although, statistically no significant association of malnutrition (based on MIS>5) with latent TB, with odds ratio of 3.47 (95%CI 0.93–12.93), we consider it as clinically significant. Since no difference subjects' characteristics between positive and negative IGRA, we did not performed analysis for confounding in this study.

Variably results on the previous studies are existed about association between nutrition status and latent TB. Baek et al[7]whether hemodialysis adequacy is associated with LTBI in the ESRD population is unclear. In this study, we aimed to investigate the association between hemodialysis adequacy and LTBI in ESRD patients. METHODS: In the present cross-sectional study, we reviewed all outpatient-based ESRD patients in our artificial kidney room. Interferon gamma release assay (IGRA assessed nutrition status by normalized protein catabolic rate (nPCR) measurement and latent TB by IGRA. Nutrition inadequacy based on nPCR value less than 0.87 g/kg/day predicts latent TB among HD patients significantly. On the other hand, another study revealed no significant association between latent TB and malnutrition among CKD on HD patients.[18] Using simple assessment, such as BMI only, patient with malnutrition were similarly distributed in positive and negative tuberculin skin test subjects. [19]

This study used cut-off >5 of to determine malnutrition in this study. It refers to some previous studies. Another study revealed that MIS score higher than 7 can be able to predict mortality for 18–24 months follow up.[20] It indicates that MIS > 5 has significant risk for 1-year mortality. MIS >5 also used by Harvinder et al on HD and peritoneal dialysis patients. With this cut-off and compared to established guidelines by International Society of Renal Nutrition and Metabolism for Protein Energy-Wasting, MIS had modest sensitivity detect malnutrition in dialysis patients (60–80%).[4] Further diagnostic analysis with higher sample size might be required to support and reveal the fixed and better diagnostic value for MIS cut-off.

As a limitation, our study is merely cross-sectional study. Hence, this is a snapshot representation of association between latent TB and malnutrition, as well as could not determine causal inference of those. Furthermore, other more objective malnutrition assessment tools might be required to accompany the MIS one. As mentioned above, MIS has subjective components of medical history taking that can biased by some condition that commonly occurred in CKD on HD patients, such as depression, fatigue, and cognitive disturbance. These probably affects the assessment. However, our study is the first documentation in Indonesia that investigates the association of nutrition status based on MIS with latent TB among CKD on HD patients. MIS could be used as detection tools of latent TB, even though the further validation and diagnostic investigation are required. Further study to evaluate the causal inference of latent TB and malnutrition is needed.

In conclusion, malnutrition according to MIS > 5 is not statistically associated, but clinically associated with latent TB infection based on IGRA positivity. Further causal inference study is needed to determine, strengthen, and re-evaluate this association.

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Glioblastoma following Hemorrhagic Stroke: A Case Report

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pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n1.2142
IJIHS. 2021;9(1):36–41

Received:
September 21, 2020

Accepted:
March 30, 2021

Abstract

Objective: To report a glioblastoma (GBM) case preceded by a hemorrhagic stroke.

Methods: This case reported a 53-year-old male presenting at at Murni Teguh Memorial Hospital, Medan, Indonesia, with a chief complaint of an altered mental state. The condition had been worsened for two weeks. On anamnesis, he was identified to have experienced intracerebral hemorrhage in January 2020. A follow-up head computed tomography scan was conducted in September 2020, showing a normal condition of the brain. Other oncogenic risk factors were not found. Due to convulsion in October 2020, the patient underwent a magnetic resonance imaging examination showing a cystic right temporoparietooccipital lesion and cerebral edema. Craniotomy tumor removal surgery was performed while the tumor was further examined for histopathological findings. The tumor was diagnosed as glioblastoma with microvascular proliferation and palisading necrosis.

Results: There was some associations between hemorrhagic stroke and glioblastoma development.

Conclusion: GBM preceded by hemorrhagic stroke is a rare case that can be diagnosed thoroughly by complete clinical and adjunct examinations.

Keywords: Brain tumor, glioblastoma, hemorrhagic stroke

Introduction

Stroke is a type of neurovascular disease that still remains as one of the major causes of disability, morbidity, and mortality in Indonesia.[1] Indonesian Basic Health Research (Riset Kesehatan Dasar) in 2018 reported that the prevalence of stroke increased as compared to 2013.[2]

Stroke is classified into ischemic and hemorrhagic one while the manifestation itself depends on the brain area involved. Ischemic stroke occurs when brain blood vessels were, either partially or totally, occluded by thrombus or embolus. On the other hand, hemorrhagic stroke occurs when the blood vessels in brain parenchyma rupture and the blood disseminates into subarachnoid space.[3] Furthermore, ruptured blood vessels induce hypoxic condition in the distal area of the ruptured vessels due to diminished blood vessels capability in delivering oxygenated blood. Hence, this hypoxic area lately may cause other brain cellular changes since neurons are highly oxygen-dependent cells in nature.[1]

Glioblastoma (GBM) is one of the most common primary malignant brain tumors. Due to its distinct biology and recurrence rate, the disease prognosis is poor despite optimal treatment such as surgical resection and aggressive adjuvant treatment were conducted.[4] GBM showed angiogenesis induced by vascular endothelial growth factor hypersecretion implying its invasiveness character. Correspond to its invasiveness nature, this tumor is challenging to be resected totally.[5] The advances of GBM

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biology and pathophysiology are critical to allow various novel therapeutic modalities including targeted therapy, gene therapy, and immunotherapy.[4]

GBM and hemorrhagic stroke are two different diseases. The GBM risk may increase in hemorrhagic stroke patients.[6] This study reported a case of 53-year-old male diagnosed with GBM with a hemorrhagic stroke history.

Case

An otherwise healthy 53-year-old male revealed that in 2 January 2020 he had brain surgery. Before that time, he presented spontaneous loss of consciousness and, subsequently, was diagnosed with intracerebral hemorrhage based on Head CT scan examination (Fig. 1).

Decompressive craniectomy was done for the lesion and skull reimplantation was performed 3 months afterward. He received a standardized herbal medicine namely Neuroaid®. After skull reimplantation, he fully recovered and completed the treatment. In September 2020, a follow up Head CT scan was performed and the conclusion was normal (Fig. 2).

In October 2020, he presented 2-weeks history of progressively worsening convulsion, and described it as rigidity in his body and drop afterward. Following convulsion, he vomited in projectile description, suggesting an intracranial mass. The complaint did not precede by any other situation or condition. Oncogenic risk factors, such as genetic predisposition, previous head injury, and exposure of oncogenic agent (pesticide, rubber, radiation, and smoke) were not found in this patient.

Physical examination demonstrated somnolence sensorium with Glasgow Comma Scale Score of 12 (E4M4V4), blood pressure of 150/90 mmHg, weakness on left extremities, and right temporal craniotomy scar. Patient arrived at the hospital with the Karnofsky Performance Status Scale of 40. This study was performed preoperative contrast-enhanced brain magnetic resonance

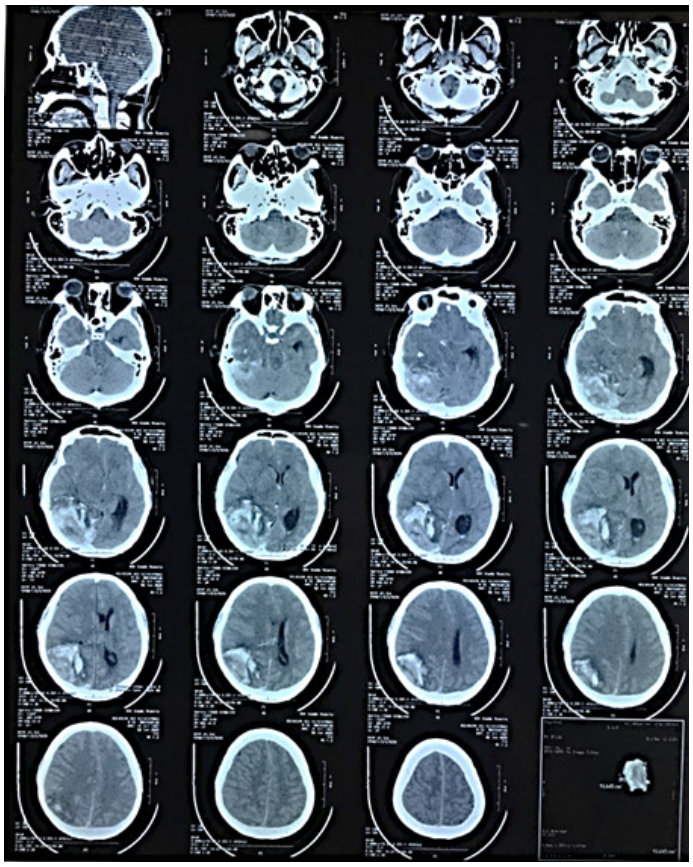

Fig. 1 Head CT Scan Showed An Intracranial Hemorrhage in Right Parietooccipital Region with Midline Shift

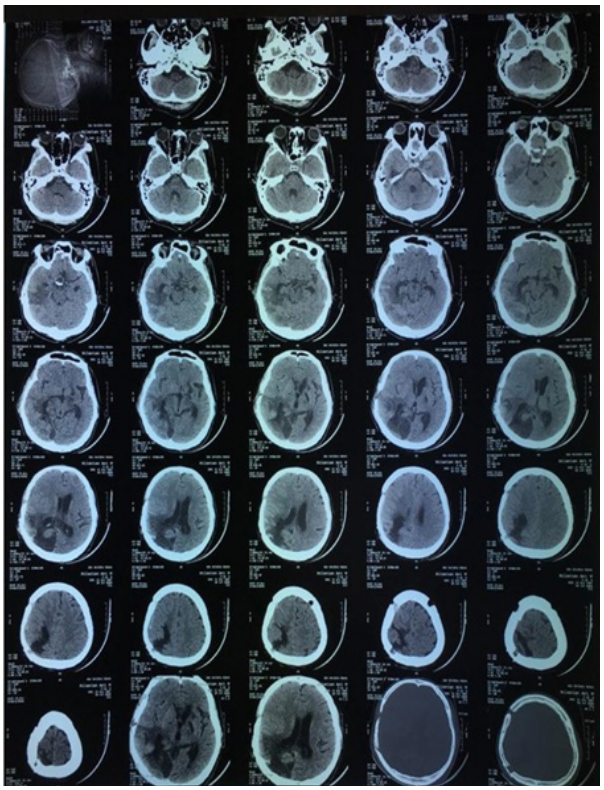

Fig. 2 Follow up Head CT Scan Showed Post Right Parietal Decompressive Craniotomy with Normal Brain Imaging Finding

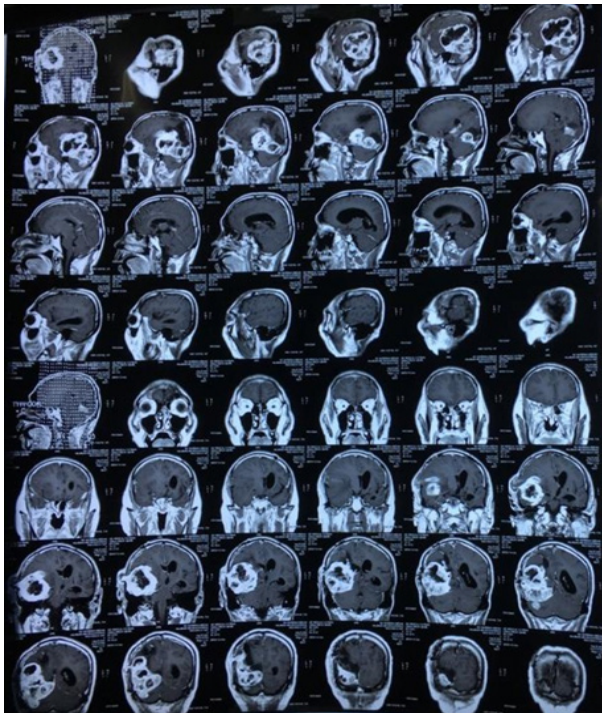

Fig. 3 Preoperative MRI Showed Cerebral Tumor on the Right Temporoparietooccipital Region that Extend to Right Cerebellum with Extracranial Protrusion from Craniotomy Remnant

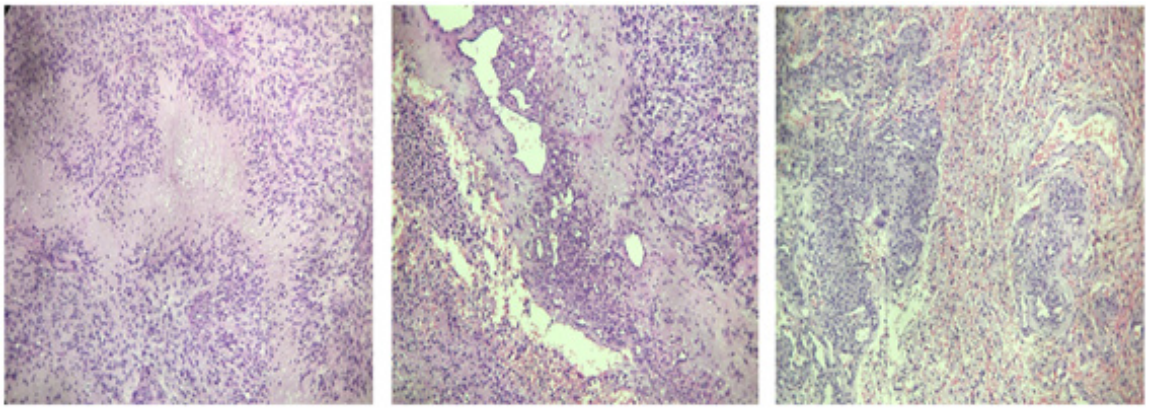

Fig. 4 Histopathological Appearance of the Resected Specimens Showed the Palisading Necrosis (a) Garland pattern of microvascular proliferation; (b) and glomeruloid pattern of microvascular proliferation; (c) Magnification 100X, HE staining

imaging (MRI). The radiological examination demonstrated a 6.8 × 7.1 x 8.6 cm cystic right temporoparietooccipital lesion. The lesion was surrounded by area of heterogeneous contrast enhancement extending to the right corona radiata and periventricular white matter that is associated with cerebral edema (Fig. 3). Furthermore, a mass extension to right brain stem was found.

Craniotomy tumor removal procedure was performed at supine position. Surgery was performed with incision in the previous surgical site. After opening the dura mater and bleeding control, the tumor was then removed by using piecemeal manner. The tumor removal procedure was completed but not all the tumor mass was technically resectable due to the brain stem tumor extension. The tumor had characteristic of cystic, grey and black in color, and can be suctioned during operation. The patient was hemodynamically stable during the surgery and transferred to intensive care unit for post-operative care. His condition improved post-operatively and later he was discharged from hospital. The biopsy specimen was sent for histopathology examination. Histopathological examination concluded that the brain tumor was glioblastoma with microvascular proliferation and palisading necrosis (Fig. 4).

Discussion

Epidemiological studies showed increased brain tumor incidence in previously stroke or head injury patients. Previously stroke patients could increase brain tumor development risk.[7] Ruptured blood vessels in hemorrhagic stroke result in decrease in cerebral blood flow, a mechanism for reducing bleeding, and if the hypoperfusion persists beyond several minutes, brain ischemia arises and brain cells hypoxia ensues.[8] Hypoxic condition may induce brain mesenchymal cells changes into glioma cells.[9] Ngb overexpression promoted the proliferation of neural progenitor cells (NPC), enhanced neuronal differentiation of cultured NPC under differentiation conditions, promotes neurogenesis in mice brain after stroke.[10] GBM can also considered to be developed after infarction that could possibly arising from glial scar. Hence, reactive gliosis may lead to brain tumor development, as GBM proposed to be originated from glial progenitor cells and reactive astrocytes, a type of neuroglia.[11]

When brain undergo hypoxia, neuroglobin (Ngb) is expressed by neuronal and neuroglial cells in order to increase brain cells survival.[1] Ngb, the heme-containing protein, is involved in metabolism of reactive nitrogen and oxygen species as well as in intracellular signaling pathways.[12] In cultured neural (HN33) cells lentiviral vector-mediated overexpression of the hypoxia inducible factor (HIF-1α) subunit, increased expression of HIF-1α was associated with an ~2-fold increase in the expression of Ngb.[13] VEGF and EPO contribute to hypoxia-induced Ngb up-regulation. In cortical neuron cultures, administration of VEGF increased Ngb protein expression however Ngb overexpression in turn suppressed VEGF

expression.[14] This may explain the palisading necrosis and microvascular proliferation in GBM histopathological examination (Fig. 4).

The Ngb expression also increased in human glioblastoma cells during hypoxia *in vitro*.[10] Furthermore, Ngb increase tumor survival capability via Ngb ability to enhance proliferation and inhibit apoptosis by regulating phosphatidylinositol 3-kinase (PI3K)/AKT pathway. The roles of PI3K/AKT pathway in cell proliferation, apoptosis resistance, and cell cycle progression of glioma cells, includes mTOR, Bax, cyclin D1, Bcl-2, and Bcl-2-like 1. mTOR promotes cell survival and proliferation in glioma cells. Altered expression of Bcl-2/Bax has an association with altered levels of glioma cells apoptosis.[9]

In cultured mouse astrocytes, Ngb blocks the stimulation of Bax (pro-apoptotic) and the inhibition of Bcl-2 (anti-apoptotic) expression induced by oxidative stress, and subsequently eliminates caspase 3 activation.[15] Astrocytes have the capabilities to mount antioxidative responses that allow astrocytes to cope with an ischemic environment. Ischemic condition then could activate astrocytes ischemic tolerance that further reduce future ischemic episodes damage from sub threshold ischemic insults. Area of focal brain hypoxia correlates with area of infarction that could be due to impaired reactive oxygen species elimination that result from lack of vimentin and glial fibrillary acidic protein (GFAP). GFAP upregulation indicates astrocytes reactivity found in vast neuropathology conditions such as stroke, neurotrauma, brain tumor, perinatal asphyxia, epilepsy, Parkinson's disease, Alzheimer's disease, or multiple sclerosis.[11] In an injured brain, glial cells express *glial cell-derived neurotrophic factor* (GDNF) *de novo*. In addition, neuroinflammation has been reported to induce GDNF expression in activated astrocytes and microglia, infiltrating macrophages, nestin-positive reactive astrocytes, and neuron/glia (NG2) positive microglia-like cells.[16] The potential of Ngb in astrocytes proliferation remains unclear. After brain injury, reactive astrogliosis showed molecules expression changes and astrocytes hypertrophy proliferation. Therefore, tissue damage and inflammation results in areas of glial scar, proliferating astrocytes, fibromeningeal cells and other glial cells, as well as collagen deposition in extracellular matrix.[17]

In conclusion, GBM case preceding hemorrhagic stroke is rarely reported and hard to be diagnosed. In this case report study, GBM diagnosis in this patient was confirmed by histopathological examination postoperatively.

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