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Hemorrhagic Transformation Incidence in Ischemic Stroke with Hyperthyroidism Rick Factor Accompanied by Atrial Fibrillation

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ABSTRACT

Hemorrhagic transformation (HT) is one of the most common life-threatening complications of ischemic stroke. It occurs when peripheral blood extravasates through the damaged blood-brain barrier (BBB) into the brain parenchyma after ischemic stroke. Hyperthyroidism, the most common endocrine disorder, occurs in 0.5−2% of the general population. Hyperthyroidism is known to trigger several cardiovascular system effects, one of which is the occurrence of atrial fibrillation (AF). There is a study that says that the incidence of HT in ischemic stroke patients with AF increases by 22.6%. A 48-year-old man with complaints of weakness of the left arm and leg, dysarthria and dysphagia with onset 2 hours before coming to the emergency department. Radiological examination showed bleeding with surrounding infarction and hyperthyroidism with AF was found. Hyperthyroidism is associated with AF which will increase the incidence of extensive ischemic stroke and the risk of experiencing HT due to damage to the BBB.

Keywords: Hemorrhagic transformation (HT); ischemic stroke; hyperthyroidism; atrial fibrillation (AF); risk factors

INTRODUCTION

Hemorrhagic transformation (HT) is one of the most common life-threatening complications of acute ischemic stroke. HT that occurs after ischemic stroke is characterized by the appearance of cerebral bleeding in the infarct area on radiological images.[1] This occurs when peripheral blood extravasates through the damaged blood-brain barrier (BBB) into the brain parenchym after ischemic stroke.

There are several predictors that can increase the incidence of HT, including massive cerebral infarction, infarction area, atrial fibrillation (AF) and cerebral embolism, high National Institute of Health Stroke Scale (NIHSS), low total and LDL cholesterol, low platelets, poor collateral vessels, thrombolytic therapy and thrombectomy, low Alberta Stroke Program Early CT Score (ASPECTS), hyperdense middle cerebral artery sign (HMCAS),[1] age, and hypertension.[2]

Patients with ischemic stroke and AF are at high risk for HT. The risk of TH is five times higher in patients with AF than in those without AF.[3] It is known that the risk of AF increases when patients have hyperthyroidism.

Hyperthyroidism, the most common endocrine disorder, occurs in 0.5–2% of the general population. Hyperthyroidism is known to trigger several cardiovascular effects, such as decreased vascular resistance, increased cardiac systolic and diastolic function, and directly increased cardiac contractility and heart rate. It can also increase the risk of arrhythmias,

especially AF.[4] In hyperthyroidism, the risk of AF increases if the patient is male, elderly, has coronary heart disease, congestive heart failure, and heart valve disease.[5] AF is the most common heart condition associated with hyperthyroidism; its prevalence is around 10–25% in hyperthyroidism compared to 1.5–2% in the general population. Recently, several studies have suggested that high free thyroxine (FT4) is associated with an increased risk of cardiovascular disease, including atherosclerosis and stroke.[6] There are not many studies that observe hyperthyroidism directly causing HT.

Through this case study, we present a case of HT in ischemic stroke with risk factors of hyperthyroidism accompanied by AF. Prevention of HT is very important to avoid clinical deterioration and increased stroke mortality.

CASE REPORT

A 48-year-old man with complaints of weakness in the left hand and leg while resting, still able to contact and follow commands well, but unclear speech articulation (dysarthria) and difficulty swallowing (dysphagia) with onset 2 hours before coming to the emergency room (ER). The patient had a history of experiencing the same complaint one month earlier and was diagnosed with non-hemorrhagic stroke with computed tomography (CT) lacunar infarction in the right insular region with an ASPECTS score of 8 (**Figure 1**). At that time the patient came to the ER after the onset was > 4.5 hours so that the patient was not given thrombolytics and therapy was carried out medically and during treatment there was no worsening of the condition. The current weakness is more severe than the previous stroke. The patient has no history of hypertension or diabetes mellitus. The patient has a history of weight loss from 85 kg to 55 kg over the past one year which was only reported after the second attack stroke, even though the food intake had been very high. The patient felt a lump on the right front neck which had only been felt for one month. Initially the lump was small and gradually enlarged. Sometimes the chest feels palpitations. The patient's clinical condition is as shown in **Figure 2**. After the first stroke treatment, the patient received home therapy with citicoline 2x500 mg, aspirin 1x80 mg and clopidogrel 1x75 mg (2 weeks of administration). There were no complaints of headache, nausea or vomiting.

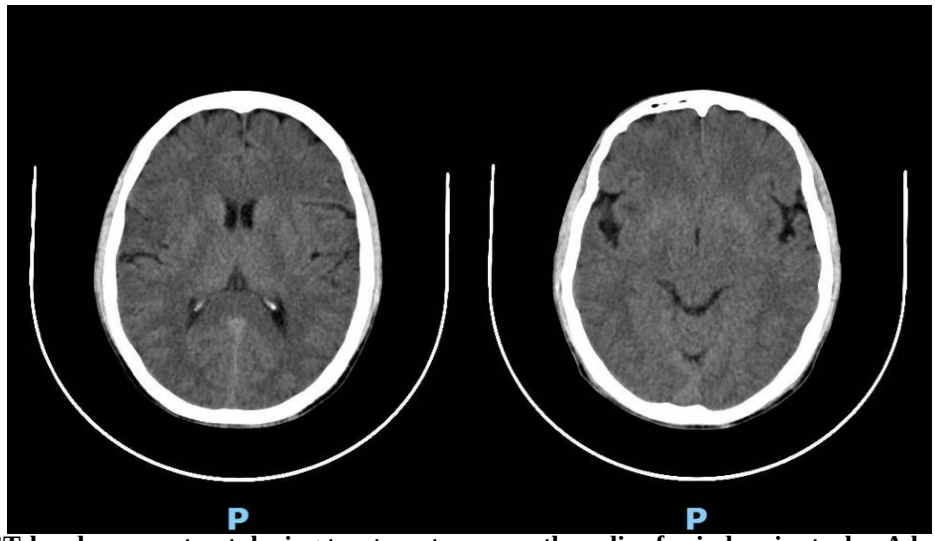


Figure 1 | CT-head non-contrast during treatment one month earlier for ischemic stroke. A lacunar infarct was found in the right insular region.

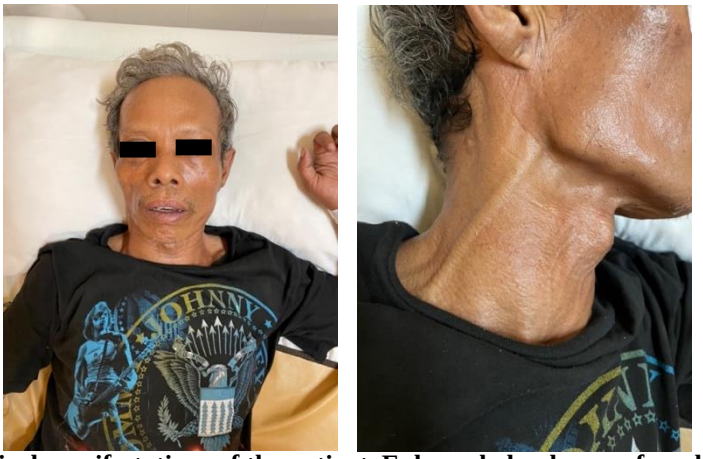
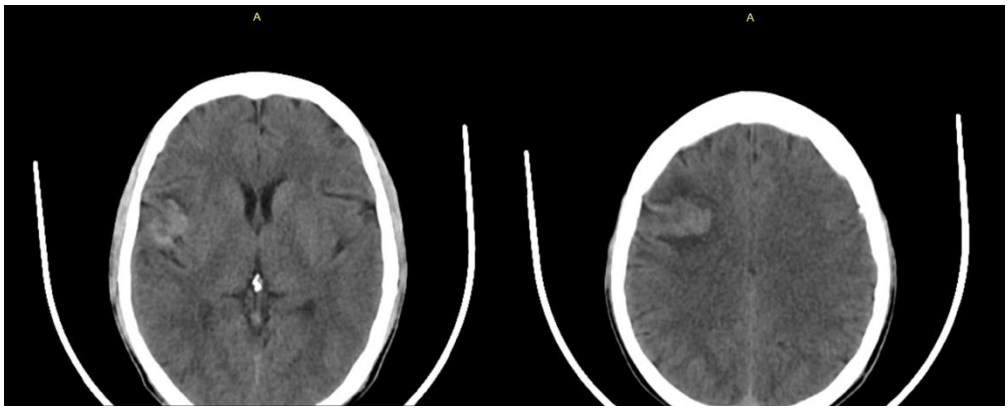


Figure 2 Current clinical manifestations of the patient. Enlarged glands were found in the anterior neck.

On physical examination, the consciousness was found to be compos mentis with an irregular pulse of around 106−188 times per minute. Neurological examination found supranuclear type left N. VII paresis, supranuclear type left N. XII paresis accompanied by dysphagia. There were no signs of meningeal irritation, there was left hemiparesis grade 3 according to the Medical Research Council (MRC) scale. Sensory examination found left hemihypoesthesia. The physiological reflexes on the left side of the body seemed to be increased and a positive Babinski reflex was found on the left leg. The NIHSS score on arrival was 7 and the Rapid Arterial Occlucion Evaluation (RACE) score was 3. The results of electrocardiography (ECG) examination showed a rapid ventricular response AF. Laboratory test results random blood sugar 134 mg/dL, sodium 141 mmol/L, blood urea nitrogen (BUN) 10 mg/dL, total cholesterol 79 mg/dL, LDL cholesterol 38 mg/dL, HDL cholesterol 23 mg/dL, TSH 0.16 mIU/L, FT4 4.36 ng/dL. Other laboratory test results are within normal limits.

CT-head non-contrast (**Figure 3**) showed a picture of bleeding in the right insular region and right frontoparietal with a picture of infarction around it. In addition, the patient also underwent a thyroid ultrasound (**Figure 4**) and found a picture of bilateral thyroiditis and bilateral colli lymphadenopathy.



(A) (B)

Figure 3 | The results of a CT-head non-contrast showed a picture of bleeding in the right insular region (A) and right frontoparietal region with a picture of infarction around it (B).

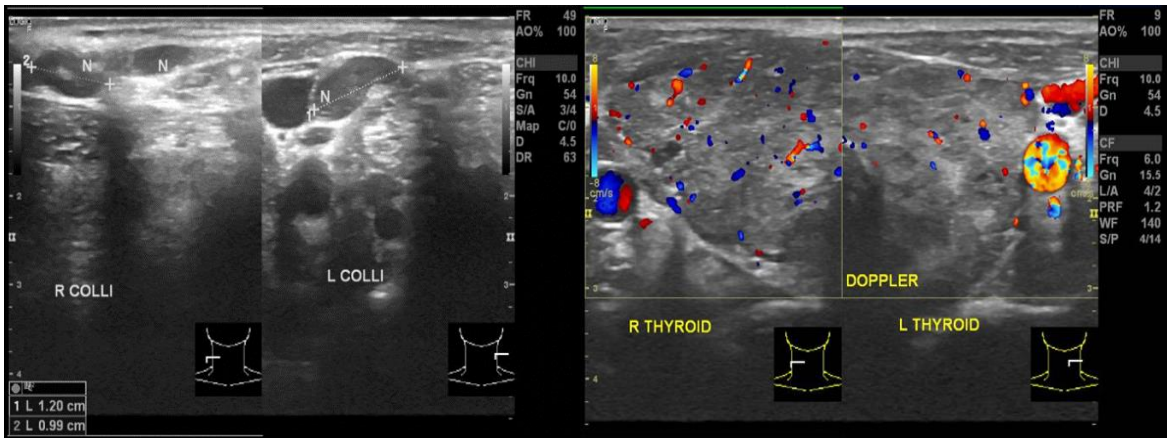


Figure 4 | Thyroid USG results. Bilateral thyroiditis and bilateral colli lymphadenopathy were found.

Our patient was diagnosed with HT stroke with hyperthyroidism and AF. The patient was given mannitol 20% therapy with a dose of 6 times 100 mL then decreased the dose by 100 mL every day, and amiodarone therapy 150 mg for 10 minutes.

During intravenous amiodarone administration, vital signs, neurological deterioration and complications were closely observed. After 10 minutes of amiodarone administration, there was improvement in complaints to no longer palpitations, ECG examination became normal sinus rhythm and there was no deterioration in neurological function. Amiodarone administration was continued with a dose of 360 mg for 6 hours and then continued again with 540 mg for the next 18 hours.

The patient was treated in a general ward and further treatment was carried out conservatively using mannitol 20% which was reduced in dose every day, intravenous tranexamic acid 3 times 500 mg, intravenous citicoline 2 times 500 mg, oral amiodarone 3 times 200 mg, oral bisoprolol 1 time 1.25 mg and oral thiamazole 2 times 10 mg. During the recovery period, the patient underwent rehabilitation with physiotherapy and active and assistive facial and extremity muscle exercises.

After treatment and physiotherapy, the patient's motor strength became 4 in the upper and lower extremities. Facial weakness began to improve and speech was better than before. There was no more AF during treatment.

When discharged, based on clinical and physical examination, the patient experienced an improvement in the NIHSS score to 5. Assessment based on the Glasgow Outcome Scale Extended (GOSE) obtained a score of 8 (upper good recovery) and Modified Rankin Scale 2. The patient was able to mobilize actively. Physiotherapy was still carried out every 2 weeks to 2 months after the stroke.

Future monitoring of the patient could not be carried out because the patient did not return to the polyclinic at our place for further patient monitoring.

DISCUSSION

HT is a complex phenomenon. Within seconds to minutes after the onset of cerebral ischemia, there is a decrease in the amount of ATP and a decrease in the activity of Na^+-K^+ ATPase. This causes a series of cellular and metabolic imbalances that result in the breakdown of the BBB. The breakdown of the BBB increases vascular permeability and extravasation of blood vessel components.[7]

Inflammation and immune system activation are also important contributors to BBB damage in HT. In acute stroke, neutrophils and monocytes are activated to produce reactive oxygen species (ROS) and matrix metalloproteinases (MMP-2, MMP-9) that contribute to BBB damage, especially

18−24 hours after onset. During this molecular process, MMP-9 has been shown to play a key role in the damage of basal lamina type IV collagen.[8] Damage to the basal lamina causes macromolecules to leak into the interstitial fluid of the central nervous system. This is also known as vasogenic edema. Microglia, astrocytes, and endothelial cells also contribute to BBB damage in HT through the production of MMPs, proteases, vascular remodeling, and neuroinflammation.[9] In conclusion, a high neutrophil-lymphocyte ratio is a biomarker of systemic inflammation. High neutrophils indicate increased release of MMP-9 and damage to the neurovascular unit and BBB integrity, increasing the risk of HT.[10]

HT can be predicted based on clinical symptoms (NIHSS) and CT or MRI findings within 48 hours after the onset of ischemic stroke.[11] So far, there have been no case studies reporting HT in subacute stroke, especially with risk factors for hyperthyroidism. Hemodynamic stabilization should be performed immediately as the first step in HT management, followed by intensive care if available. To evaluate the mechanism of HT, it is necessary to find out what risk factors cause HT in patients.[11]

Several studies have suggested that HT does not have a serious negative effect on the clinical outcome of patients, because many cases of HT, including petechial hemorrhage, are asymptomatic. However, the prognosis of HT depends on its type. Mild to moderate HT has a good prognosis if adequate therapy is given.[12] Only severe HT often causes rapid neurological deterioration.[13]

Although all risk factors have been well documented in several randomized controlled trials (RCTs), the underlying mechanisms of HT are still poorly understood.[14] There is a strong relationship between the duration and severity of cerebral ischemia and the risk of HT in stroke patient groups and experimental stroke models. The longer onset of stroke without therapy is associated with the large infarct volume, severe vascular damage and the risk of HT. In addition, reperfusion therapy is also a factor in the occurrence of HT, the earlier reperfusion therapy is given, the lower the risk of HT. Worsening NIHSS is also associated with the occurrence of HT. Patients with NIHSS < 10 have a risk < 13% of HT. While patients with NIHSS > 15 have a risk > 50% of HT.[15] A prospective study with 234 ischemic stroke patients with AF conducted by Fahmi *et al*., said that the incidence of HT in ischemic stroke patients with AF was 22.6%. Univariate analysis determined that elderly, hypertension, diabetes mellitus, using anticoagulants, NIHSS and infarct size were significant main predictors in HT cases.[16] In this case, the patient had a history of ischemic stroke one month earlier, but the infarct volume was not large and did not receive reperfusion therapy, the patient's current NIHSS score was also mild, but the patient had risk factors for hyperthyroidism with AF that were suspected to have occurred before the previous ischemic stroke. It is possible that the previous ischemic stroke was caused by risk factor of hyperthyroidism. There was no previous ECG data indicating the presence of AF due to limited access to medical records. However, there have been no studies or literature on hyperthyroidism with AF as a risk factor for subacute ischemic stroke transformed into hemorrhagic.

Hyperthyroidism significantly increases the incidence of AF, as demonstrated by a meta-analysis study by Collet *et al*.[17] Although the association between hyperthyroidism and several risk factors for stroke has been demonstrated, the risk of stroke due to hyperthyroidism remains unclear. Hyperthyroidism has been shown to be an independent risk factor for ischemic stroke, especially within the first year of hyperthyroidism diagnosis. However, the association became insignificant over subsequent years. The incidence of bleeding was lower in hyperthyroidism with AF compared to AF without hyperthyroidism. The finding of the highest incidence of

ischemic stroke within the first year of hyperthyroidism diagnosis in the AF population is similar to a Danish population-based cohort study in which a high risk of ischemic stroke occurred within the first 3 months after hyperthyroidism diagnosis in the general population, which has an underreported prevalence of AF.[18] Similarly, a recent study in Korea identified an increased risk of thromboembolism within the first year of hyperthyroidism diagnosis with AF.[19] In another cohort study including 160 hyperthyroid patients with AF, the majority of ischemic strokes occurred within the first 30 days after AF was detected.[20] In conclusion, hyperthyroidism is an independent risk factor for ischemic stroke in patients with AF, especially within the first year of hyperthyroidism diagnosis.[21]

Based on existing sources, it can be concluded that low FT4 changes the hemostasis system towards hypocoagulation and hyperfibrinolysis which increases the risk of bleeding but protects against thromboembolic events. In contrast, high FT4 leads to hypercoagulation and hypofibrinolysis which increases the incidence of thromboembolism. Fibrinogen, factor VIII and von Willebrand factor (VWF) are important players in the coagulation process of hyperthyroidism.[22] Several research results have shown that increased FT4 can also cause atherosclerosis, endothelial dysfunction and hypercoagulation which leads to thromboembolism.[18,23,24] Hyperthyroidism also increases the risk of AF by 2.3 times compared to the normal population.[24] In addition, a cohort study found that hyperthyroidism is associated with an increased incidence of stroke. The risk of hemorrhagic stroke is not much different between hyperthyroidism and controls.[25] In contrast, a study conducted by Marouli *et al*., said that there is no causal relationship between hyperthyroidism and stroke.[6] A multicenter study of 43,598 patients to find the relationship between variations in thyroid function and the risk of stroke. The study showed that high thyroid stimulating hormone (TSH) is associated with a decreased risk of stroke due to a decreased risk of AF, while low TSH and high FT4 are associated with an increased risk of AF, which will cause cardioembolic stroke.[26] In this case, the patient experienced HT from an ischemic stroke that had occurred one month earlier and when examined in the laboratory, TSH was lower than normal and FT4 was high. This is inconsistent with the findings of previous studies that hyperthyroidism actually has a low risk of bleeding. In contrast, hypothyroidism has a high risk of bleeding due to decreased coagulation factors. Coagulation factor examination cannot be done because there are no examination facilities. However, the patient has low total cholesterol and LDL which are risk factors for bleeding.[1]

Several studies have suggested that inhibition of MMP-2 or MMP-9 can reduce the risk of HT during the early stages of cerebral ischemia. It has been described that both MMP-2 and MMP-9 are significantly increased and activated during the early stages of cerebral ischemia lesions. High levels of both enzymes can increase the incidence of HT. Therefore, decreasing the activity of MMP-2 and MMP-9 can reduce the incidence of HT.[27] Phosphodiesterase-III inhibitors can prevent the development of HT, reduce brain edema, prevent endothelial lesions by reducing MMP-9 activity, and prevent increased BBB permeability.[28] In addition, thiamine is also a therapy that can reduce MMP-2 and MMP-9 levels.[29] In this case, the patient received therapy according to the case of bleeding. Mannitol 20% was given to prevent increased intracranial pressure, tranexamic acid to prevent the amount of bleeding that occurs. Thiamazole was given because of hyperthyroidism, on the other hand, it can prevent thrombosis due to hyperthyroidism.[30]

Vascular compression may also occur in hyperthyroidism with thyroid nodules. Goiter may cause venous stasis or reduction in cerebral arterial blood flow due to carotid compression. There is at least 1 report of a

patient with goiter who had compression of the brachiocephalic vessels and no other factors that could have caused the condition. This patient had goiter and left hemiparesis due to right temporoparietal infarction. Cerebral arteriography showed secondary stenosis of the brachiocephalic and right subclavian vessels due to compression by the thyroid nodule.[31]

The hemorrhagic risk stratification score (HeRS) is a good predictor for HT cases in ischemic stroke patients with indications for anticoagulant administration. This is evident from an independent prospective cohort study conducted by Marsh *et al*., where the indicators of this score include infarct volume, age and renal impairment.[32]

CONCLUSION

HT is a complex and multifactorial phenomenon, so many etiological aspects need attention. More attention is needed for patients with acute cerebral infarction, especially those with several risk factors mentioned above. Management of patients with acute cerebral infarction requires special attention to avoid HT events, CT and MRI are needed periodically. In addition, prevention and therapy of HT are still unclear. So there are still many obstacles in research related to HT cases, so further research is needed.

Physicians should be aware of the possibility of hyperthyroidism as an underlying disease for hemostasis disorders. In addition, in patients with AF, high NIHSS scores, elderly should be considered as a high-risk category for HT.

Early detection and adequate management are essential for patients with hyperthyroidism to prevent complications that can increase morbidity and mortality. Accurate diagnosis of hyperthyroidism in ischemic stroke patients is a challenge because of overlapping clinical features with other medical conditions. Regular TSH checks in patients with AF are recommended.

There are not many studies that observe the occurrence of HT in ischemic stroke cases with risk factors for hyperthyroidism, especially subacute ischemic stroke onset. Despite these limitations, several existing sources state firmly that thyroid hormone disorders, AF, and age are important predictors of HT. Further studies are needed and focus on the relationship between hyperthyroidism and the occurrence of HT in ischemic stroke cases.

Declaration by Authors

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