Pineal Calcification is Associated with Symptomatic Cerebral Infarction

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Background: Pineal calcification and low melatonin have been shown to be risk factors for stroke in animal studies; however, there are limited clinical data on the association of pineal calcification and stroke in humans. *Methods:* All computed tomographic (CT) scans of the brains of patients >15 years of age during the year 2011 at a university teaching hospital were retrospectively reviewed. Patient medical charts were used to obtain the risk factors for stroke, including diabetes, hypertension, dyslipidemia, age, and sex. Cerebral infarction was identified by having clinical syndromes of stroke and a positive CT scan. Patients with embolic or hemorrhagic stroke were excluded. Pineal calcification was evidenced by the CT scans. The association of various stroke risk factors and cerebral infarction were calculated using logistic regression analysis. *Results:* A total of 1614 patients were included, and symptomatic cerebral infarction was identified in 620 patients (38.4%). Regarding stroke risk factors in symptomatic cerebral infarction patients, the majority of patients were male (356 [57.4%]), >50 years of age (525 [84.7%]), and had hypertension (361 [58.2%]); some had diabetes (199 [32.1%]) and dyslipidemia (174 [28.1%]). Pineal calcification was found in 1081 patients (67.0%), with a male:female ratio of 1.5:1. Significant factors related to cerebral infarction by univariate logistic regression were age >50 years, hypertension, diabetes, dyslipidemia, and pineal calcification. Pineal calcification as a risk factor for cerebral infarction had an adjusted odds ratio of 1.35 (95% confidence interval 1.05-1.72). *Conclusions:* Pineal calcification may be a potential new contributor to cerebral infarction. **Key Words:** Cerebral infarction—melatonin—pineal calcification—predictors—risk factor.

The pineal gland is located at the posterior part of the third ventricle. Its main function is to secrete melatonin, a neuroendocrine hormone that is essential for maintaining the phase relationships between oscillators in the central nervous system and in peripheral organs (i.e., controlling the circadian rhythm and the sleep–wake pattern in humans).[1] It also has many other effects, including anti-inflammation,[2] immune response,[3] antioxidant,[4,5] and neuroprotection.[6-8]

Melatonin secretion declines with age,[9,10] and this decrease is associated with a variety of neurodegenerative diseases, such as Alzheimer disease,[11] Parkinson disease,[12] epilepsy,[13] depression,[14] stroke,[15] and cancer.[16] Melatonin deficit has been hypothesized to be caused by pineal

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calcification. Pineal calcification is a process whereby calcified concretions of hydroxyapatite develop; this calcification is observable by imaging techniques such as computed tomography (CT).[17,18]

Calcification is thought to be caused by cellular degeneration and death,[19,20] increasing with age, and is typical in adults. It has been observed in children as young as 2 years old,[9] with calcification rates estimated to be 40% for children in their late teens[17,21] and >70% after 40 years of age.[21] Reported calcification rates vary widely by country,[22-24] but the prevalence is lower in Africans and African Americans.[22,23]

Levels of 6-sulfatoxymelatonin, the main metabolite of melatonin, have been shown to positively correlate with the size of uncalcified pineal tissue, adjusted for age and sex ($P = .002$).[7] Pineal calcification has also been associated with various diseases, including multiple sclerosis, schizophrenia,[25] affective disorders,[26] and sleep disorders.[27] Recently, patients with Alzheimer disease have been shown to have significantly lower uncalcified pineal tissue ($P = .027$) and a higher degree of pineal calcification ($P = .001$) than healthy elderly subjects.[28]

A single study has reported a high frequency of pineal calcification in patients with stroke compared to healthy subjects.[29] Because of the neuroprotective properties of melatonin, it is postulated that pineal calcification causes a melatonin deficit, which in turn could increase the risk for stroke. Previous animal and human studies have also shown that melatonin treatment after stroke reduced brain damage and has preferable stroke outcome.[30,31]

This study aimed to evaluate the association of pineal calcification and cerebral infarction using CT scans of the brain and controlling for known confounding factors, such as age, sex, and underlying disease.

Methods

All CT scans of the brains of patients >15 years of age in the year 2011 at Srinagarind Hospital, Khon Kaen University, Thailand were retrospectively reviewed. Patient medical charts were used to obtain the risk factors for cerebral infarction, including diabetes, hypertension, dyslipidemia, age, and sex. Diseases were recorded when diagnosed by physicians. Dyslipidemia was defined by the presence of one of the following findings: total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >100 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL. Pineal calcification was identified on CT scans of the brain (Fig 1). Cerebral infarction was diagnosed by having any symptoms of stroke syndrome and evidenced by a CT scan of the brain. We excluded patients with embolic or hemorrhagic stroke, those with pineal glands that were unable to be evaluated from the CT scans, or those without medical charts. The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research.

The prevalence of pineal calcification and cerebral infarction was calculated. The association of various stroke risk factors and cerebral infarction was calculated using univariate logistic regression analysis. Potential factors (i.e., sex, age, hypertension, diabetes, and dyslipidemia) were included in a multiple logistic regression analysis for cerebral infarction. $P < .05$ was considered statistically significant. All statistical analyses were performed using Stata software (version 10.1; StataCorp, College Station, TX).

Results

The total number of CT scans of the brain included in the study period was 2140. Of those, 195 patients were <15 years of age, 189 had embolic or hemorrhagic stroke, 116 patients had insufficient chart data, and 26 scans were of poor quality on pineal gland evaluation. There were 1614 patients that met the required criteria for evaluation.

The mean age of the patients was 55.5 years (SD 17.5) years. There was no sex difference (885 men [54.8%] and 729 women [45.2%]). Cerebral infarction was identified in 620 patients (38.4%). This incidence of cerebral infarction increased with age, and a rate of >50% was observed in patients >60 years of age (Table 1). Regarding stroke

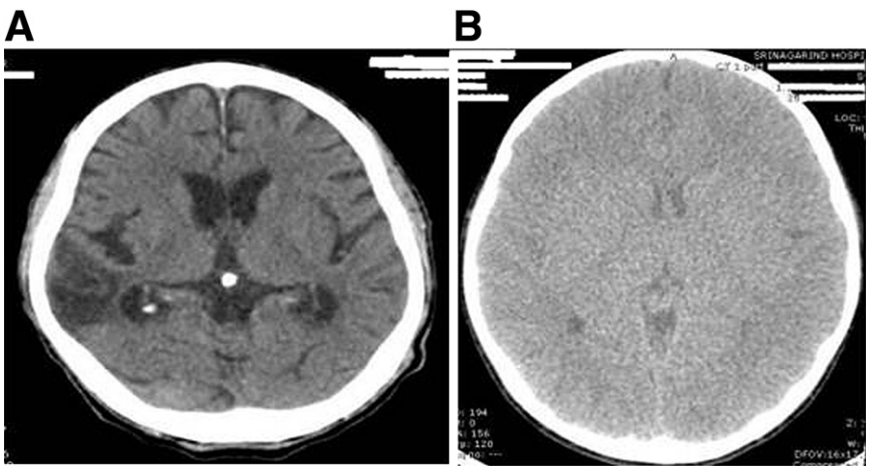

Figure 1. *Pineal calcification identified by a computed tomographic scan of the brain in a patient with cerebral infarction (A) compared to a patient without pineal calcification (B).*