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Pineal calcification is a novel risk factor for symptomatic intracerebral hemorrhage

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ABSTRACT

Background: Pineal calcification is associated with symptomatic cerebral infarction in humans. However, there are limited data on the association of pineal calcification and intracerebral hemorrhage. We evaluated this association of symptomatic intracerebral hemorrhage and pineal calcification by computed tomography of the brain.
Methods: We reviewed all computed tomographic (CT) scans of the brains of patients over 15 years of age during the year 2011 at a university teaching hospital. Symptomatic intracerebral hemorrhage was identified by having clinical syndrome of stroke and acute intracerebral hemorrhage from brain CT scans. Pineal calcification was also evidenced by brain CT scans. Other stroke risk factors were recorded. The association of various risk factors including pineal calcification and intracerebral hemorrhage was calculated using logistic regression analysis.
Results: There were 2140 CT scans of the brains during the study period. Of those, 1071 scans (50.05%) met the study criteria. Intracerebral hemorrhage and pineal calcification were found in 77 (7.2%) and 689 (64.3%) patients, respectively. Pineal calcification was a significant risk factor for intracerebral hemorrhage with an adjusted odds ratio of 2.36 (95% confidence interval of 1.22-4.54). Other significant factors were age > 50 years, hypertension, and diabetes.
Conclusion: Pineal calcification is associated with symptomatic intracerebral hemorrhage.

1. Introduction

Pineal calcification can be identified by non-contrast computed tomography of the brain. The prevalence of pineal calcification increases with age and this observation is found similarly in different parts of the world [1–4]. Pineal calcification is related to low levels of the urine metabolite of melatonin (6-sufatoxymelatonin) indicating a decreased production on melatonin by calcified glands [3]. Melatonin plays important roles in circadian rhythm, sleep and is also a powerful antioxidant [5–8].

Pineal calcification in humans is associated with symptomatic cerebral infarction with adjusted odds ratio of 1.35 (1.05–1.72) [9]. Melatonin supplement reduced brain infarction and neurological deficits in animal meta-analysis study [8]. Its supplement also improved intracerebral hemorrhage in rats [10]. The study was done in 76 rats which had intracerebral hemorrhage by the infusion of clostridial collagenase into the right caudate putamen. A three day course of melatonin had better long term outcomes in memory ability and volume of brain atrophy at 8 and 10 weeks, respectively [10]. However, short term outcomes such as brain edema or neurological symptoms at day 1 were not improved, although melatonin did reduce oxidative stress. Data however are limited in human research. Here, we investigated whether pineal calcification is associated with intracerebral hemorrhage in humans.

2. Methods

All CT scans of the brains of patients over15 years of age in the year 2011 at Srinagarind Hospital, Khon Kaen University,

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Table 1
Pineal calcification and cerebral infraction.

Age group (years)	CT brain scans, *N*	Pineal calcification, *N* (%)	Intracerebral hemorrhage, *N* (%)
16–19	53	16 (32.2)	0 (0.0)
20–29	95	44 (46.3)	0 (0.0)
30–39	133	77 (57.9)	1 (0.8)
40–49	200	138 (69.0)	9 (4.5)
50–59	199	133 (66.8)	28 (14.1)
60–69	196	140 (71.4)	16 (8.2)
70–79	144	106 (73.6)	18 (12.5)
80–89	49	34 (69.4)	5 (10.2)
≥90	2	1 (50.0)	0 (0.0)
Total	1071	689 (64.3)	77 (7.2)

Thailand were retrospectively reviewed. Patient medical charts were used to obtain the risk factors for intracerebral hemorrhage, including diabetes, hypertension, dyslipidemia, age, and gender. 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 and intracerebral hemorrhage were identified on CT scans of the brain by a neurosurgeon who had more than 10 years experience. Patients who had intracerebral hemorrhage must have had symptoms such as hemiparesis, hemiplegia, or severe headache. To avoid confounding factors such as cerebral infarction or bleeding from other causes, other potential confounding factors needed to be excluded. Exclusion criteria were those with intracerebral hemorrhage that caused by trauma, cerebral aneurysm, ruptured arteriovenous malformation (AVM), or anticoagulant therapy. Patients with embolic or ischemic stroke and those whose pineal glands were unable to be evaluated from the CT scans, or those with incomplete medical charts were also excluded. The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research.

The prevalence of pineal calcification and intracerebral hemorrhage was calculated. The association of various stroke risk factors and intracerebral hemorrhage was calculated using univariate logistic regression analysis. Potential factors (i.e., gender, age, hypertension, diabetes, and dyslipidemia) were included in a multiple logistic regression analysis for intracerebral hemorrhage. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata software (version 10.1; Stata Corp, College Station, TX).

3. Results

The total number of CT scans of the brain included in the study period was 2140. Of those, 620 patients had cerebral infarction [9], 195 patients were under 15 years of age, 112 had embolic stroke or intracerebral hemorrhage from other causes as mentioned in the exclusion criteria, 116 patients had insufficient chart data, and 26 scans were of poor quality on pineal gland evaluation. There were 1071 (50.1%) patients that met the required criteria for evaluation (Fig. 1).

The mean age of patients was 51.6 years (SD 17.9 years). There was no gender difference (578 men [54.0%] and 498 woman [46.0%]). Intracerebral hemorrhage was identified in 77 patients (7.2%). The rates of intracerebral hemorrhage dramatically increased in age group after 50 years (Table 1). Regarding intracerebral hemorrhage risk factors, the majority of patients were male (49 [63.0%]), were older than 50 years of age (65 [84.4%]), and had hypertension (57 [74.0%]); some had diabetes (18 [23.4%]) and dyslipidemia (16 [20.8%]; Table 2). Pineal calcification was found in

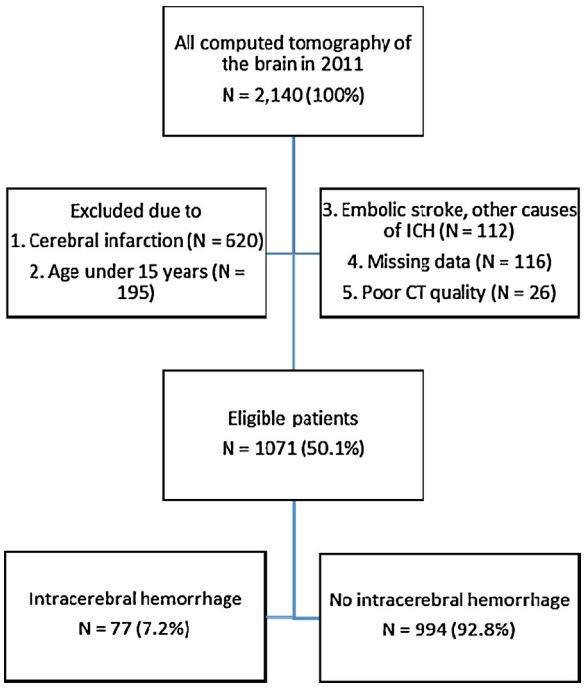

Fig. 1. Flow chart shows patient enrollment and exclusion.

689 patients (64.3%) and increased with age, with a rate of >60% for patients aged 40–89 years (Table 1).

Significant factors related to intracerebral hemorrhage by univariate logistic regression were age over 50 years, hypertension, dyslipidemia and pineal calcification (Table 2). All factors were included in multiple logistic regression analysis. Pineal calcification was a significant risk factor for intracerebral hemorrhage with an adjusted odds ratio of 2.36 (95% confidence interval of 1.22-4.54). Other significant factors were age over 50 years, hypertension, and diabetes.

4. Discussion

Similar to cerebral infarction, pineal calcification is significantly associated with symptomatic intracerebral hemorrhage. The adjusted odds ratio is slightly higher than that adjusted odds ratio for cerebral infarction; 2.36 in intracerebral hemorrhage and 1.35 in cerebral infarction [9]. Hypertension is still the strongest factor associated with intracerebral hemorrhage (adjusted odds ratio 7.39) as previously reported [11]. Long standing hypertension leads to intracerebral hemorrhage by causing vasculopathy and rupture at points of small arteriole dilatation [12].

There are several mechanisms explaining the association of pineal calcification and intracerebral hemorrhage. Melatonin supplement reduced blood pressure, heart rate, and plasma rennin activity in spontaneously hypertensive rats (SHR) [13]. Another study also showed that the reduction of blood pressure and heart rate was associated with increased endothelium-dependent vasodilatation and increased sensitivity to NO-synthase inhibitor in melatonin-treated SHR [14]. These results were confirmed in a human study where patients with essential hypertension who repeatedly took bedtime melatonin had significantly reduced nocturnal blood pressure [15].

In addition to blood pressure lowering effect, melatonin also reduced and prevented neural death. Cerebral amyloid angiopathy is the deposition of congophilic material in the media and adventitia of cortical and meningeal vessels, which can lead to necrosis of the vessel wall and hemorrhage [12,16]. Melatonin protects neurons