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Abstract. – OBJECTIVE: The pineal gland calcifications have been associated with some diseases such as cerebral infarction, Alzheimer’s disease and intracerebral hemorrhage while most cases are considered idiopathic and physiologic. However, there are limited data in the current literature about the association of pineal calcification and migraine. Our aim was to evaluate this association between migraine and pineal calcification by computed tomography of the brain.

PATIENTS AND METHODS: In our study, we assessed the computed tomography images of patients, who referred to the neurology outpatient clinic with the complaint of headache and were diagnosed with migraine without aura based according to 2004 criteria of the International Headache Society. 503 migraine patients and 500 control subjects without migraine diagnosis were included in this study.

RESULTS: When migraine and control groups were compared by pineal calcification, the rates were determined as 80.6% and 55% in migraine and control group, respectively. The difference was statistically significant ($p < 0.001$). In addition, it was seen that pineal calcifications, detected in migraine patients, did not show age-related increase.

CONCLUSIONS: According to our data, we can point that pineal calcification may be associated with migraine.

Key Words: Pineal calcification, Migraine, Computed tomography.

Introduction

Calcifications of the pineal gland were first described by Schuller in 1918. The prevalence of the calcifications, usually accepted physiologically, increases with age and shows variability between the different regions of the world. In a study performed in our country in 2008 showed that the rate of pineal gland calcifications was reported as 68.5%.

The pineal gland calcifications have been associated with reduced levels and impaired release pattern of melatonin while most cases are considered idiopathic and physiologic. Melatonin which is a hormone that released from the pineal gland has a key role that involved in regulation of the circadian rhythm and the sleep rhythm. Low melatonin level was reported to be associated with difficulty in falling asleep, frequent nocturnal awakening and sleep disorders. In addition to sleep disorders, the association among the primary headaches and melatonin secretion and pineal gland dysfunction was also established. In a study evaluating the plasma melatonin patterns in chronic and episodic headache showed that the normal pattern of nocturnal melatonin release was reported to be impaired in chronic migraine patients. Similarly, in another study, significant impairments were detected in the melatonin secretion pattern profile during the migraine status. A study by Claustre et al conducted in 93 patients with headache, showed a significant low level of plasma melatonin in migraine patients. In addition to these studies on the low levels of endogenous melatonin and migraine, there are also some studies about the usage of exogenous melatonin in the prophylaxis and treatment of migraine.

In our study, our aim was to evaluate the pineal gland calcification, associated with the reduction in the endogenous melatonin secretion, in migraine patients using computed tomography.
**Patients and Methods**

In our study, we assessed the computed tomography images of patients, who referred to neurology outpatient clinic with the complaint of headache between June 2013 and June 2014 and were diagnosed with migraine without aura based according to 2004 criteria of the International Headache Society (IHS). We were able to obtain the examination reports for all patients. Patients who were older than 15 years, had a migraine complaint for at least 6 months and had cerebral imaging reports were selected consecutively.

Patients who had a diagnosis of primary or secondary headache instead of migraine, concomitant psychiatric or mental disease or sleep disorder were excluded from the trial. The computed tomography images from 503 patients (279 females and 224 males) and 500 age and gender-matched control subjects (272 females, 228 males) with no diagnosis of headache were assessed by two different clinicians in a blinded fashion.

**Statistical Analysis**

The parametric variables were expressed in terms of mean + standard deviation, categorical variables, percentage and numbers. The parametric variables were evaluated with the Student t test in independent groups and the categorical variables with the Pearson chi-square test. p < 0.05 was considered as the limit of statistical significance; all statistical procedures were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 14.0 software.

**Results**

503 migraine patients and 500 control subjects without migraine diagnosis were included in the trial. 279 of the migraine patients were females (55.4%) while 224 were males (44.5%) and the mean age was 32.9 ± 9.6 years. The control group included 272 females (54.4%) and 228 males (45.6%) with a mean age of 33.8 ± 14.9 years. There was no statistically significant difference between the two groups by the way of mean age and the gender.

When migraine and control groups were compared by pineal calcification, the rates were determined as 80.6% and 55% in migraine and control group, respectively. The difference was statistically significant (x²: 15.256; p < 0.001). In addition, it was seen that pineal calcifications, detected in migraine patients, did not show age-related increase.

**Discussion**

We detected that the migraine patients had a significantly higher pineal gland calcification compared with control subjects. As mentioned above, the pineal calcifications did not show age-related increase in migraine patients in contrast to normal population.

Although pineal gland calcifications are usually evaluated in the group of physiologic calcifications, they have also been associated with certain disorders. Many previous disorders have been reported the association between the pineal gland calcifications and the early onset of the disease⁹, prefrontal cortical atrophy¹⁰, tardive dyskinesia¹¹,¹², dystonic motions¹³, drug-induced parkinsonism¹⁴, hallucinations¹⁵ and cognitive disorders¹⁶, particularly in schizophrenia patients. Similarly, in a study performed on Alzheimer’s patients pointed that pineal calcification grade was observed as significantly higher in the Alzheimer’s disease when compared with other groups. This was considered as potentially associated with the low circulating pure melatonin level¹⁷. In two different recent trials by Kitkhuandee et al¹⁸,¹⁹ proved that pineal calcification was claimed to be an independent risk factor for symptomatic cerebral infract (odds ratio: 1.35) and intracerebral hemorrhage (odds ratio: 2.36).

In addition to these correlations between pineal calcification and the diseases, calcifications have also been associated with the secretive dysfunctions of the pineal gland. In a study by Kunez et al², a correlation was established between the grade of pineal gland calcification and the low levels of a melatonin metabolite, 6-sulphatoxy melatonin. Therefore, it was claimed that the grade of pineal calcification could be used as an indicator of the melatonin levels. Liebrich et al²⁰ underlined the fact that the non-calcified pineal gland volume was positively correlated with the melatonin levels.

Although the ethiopathogenesis of migraine is still controversial, the impairment of the serotonin metabolism in thalamus, hypothalamus and cerebral cortex and the secondary hy-
peractivity of the trigeminovascular system are held as responsible. Dietary tryptophan passes the blood brain barrier and reaches the pineal gland. At that point, it is converted to serotonin via beta receptors in the pinealocytes in a bright environment. During the night, pineal serotonin is converted to melatonin. Serotonin, released from the pineal gland into the cerebrospinal fluid, increased the activity of the cerebral neurons; as well as it inhibits the serotonergic activity in the raphe nucleus. The reduction in the melatonin levels inhibits the raphe nucleus activity, same as the excessive serotonin levels. The raphe nucleus inhibits the trigeminovascular system, a system that leads to vasodilatation and cerebral inflammation when hyper-activated. Thus, the increased serotonin level and the reduced melatonin level are highly associated with headache, occurring secondary to the hyperactivity of the trigeminovascular system in migraine. In addition to these effects, melatonin is also known to ensure the harmony between the organism and the environment thanks to its regulatory effect on the sleep pattern, hormone secretion and the circadian rhythm. Otherwise, melatonin is known to indirectly activates the opioid receptors and reduces nociception via melatonin receptors.

The reduction in the endogenous melatonin levels and the impairment of the melatonin release patterns have also been detected in the studies of migraine patients. Also, the studies about the usage of melatonin in migraine prophylaxis are still ongoing. In one study performed in 32 migraine patients, it was revealed that the daily usage of 3 mg melatonin reduces the monthly incidence, duration, severity of headache and also the analgesic consumption. Another recent trial showed that melatonin prophylaxis in migraine could be an effective and reliable treatment method.

Conclusions

We observed that there were statistically significant higher levels of pineal gland calcifications that detected by computed tomography in migraine patients. We thought that it may be related with impaired melatonin metabolism that is considered to be involved in the pathophysiology of migraine. Further trials, also evaluating the blood melatonin levels of patients, would lead to get more elucidative data on the ethiopathogenesis and treatment of migraine.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References


