Exploring Links between Pineal Gland Calcification and Central Nervous System Disease

**Abstract:** Central nervous system disease is globally common with dysfunction of the brain and spinal cord, which significantly affects the quality of life, such as sleep disturbances. Pineal gland is pivotal in regulating sleep cycles and circadian rhythms. And melatonin, secreted by pineal gland, promotes neurodevelopment and maintains neurohomeostasis, which is also pivotal in the modulation of central nervous system disorders. In recent years, studies have found that patients with central nervous system damage often have degeneration of the pineal gland, characterized by a decrease in pineal gland volume, reduced melatonin secretion, and even parenchymal calcification. An increasing number of Alzheimer’s disease patients have been observed to exhibit pineal gland calcification. Research suggests that sleep disturbances accompanying central nervous system disorders can be attributed to the degeneration of pineal gland function, indicating a potential contribution of gland calcification to central nervous system diseases. Here, we review the recent research on pineal gland calculi and discuss the potential relationship between pineal gland calcification and various central nervous system diseases, contributing to a deeper understanding of the intricate mechanisms underlying neurological disorders.

**Keywords:** Pineal gland; calcification; pineal gland calculi; central nervous system disease.

1. **INTRODUCTION**

The central nervous system (CNS), which comprises the brain and spinal cord, acts as the central hub for consciousness, sensory perception, motor control, and higher-order cognitive process. CNS diseases present a significant challenge in contemporary healthcare, encompassing both neurodegenerative disorders and psychiatric conditions. These diseases involve intricate neural networks, giving rise to a diverse array of symptoms and functional impairments. The prevalence and complexity of CNS diseases underscore the urgent need for an in-depth understanding of their underlying mechanisms and potential contributing factors.

Recent investigations have increasingly highlighted the importance of the pineal gland in the pathogenesis of neurological disorders. Situated deep within the brain, the pineal gland is essential in the regulation of circadian rhythms and neuroendocrine function. Despite being relatively small, this pinecone-like gland holds significance due to its synthesis of melatonin and involvement in the neuroendocrine system. Over recent years, research focused on the functions and calcification of pineal gland have seen considerable growth. Pineal gland...
calcification directly impacts the number of pinealocytes, leading to insufficient melatonin secretion and consequently affecting neurodevelopment and disrupting neural homeostasis. Additionally, Studies suggest a correlation between melatonin deficiency and the deposition of Aβ, as well as damage to dopaminergic neurons, prompting further exploration into the clinical significance of pineal gland calcification. These studies aim to elucidate that pineal gland may clarify the potential involvement of the pineal gland in the onset of neurological disorders (Fig.1).

Figure 1. Pineal gland calcification plays a potential role in the pathogenesis of central nervous system disease.

2. PINEAL GLAND

The pineal gland, often referred to as the “third eye”, is red-gray, pea-like, typically 6-10 mm long, 5-6 mm wide, and weighs between 50 and 150 mg (Harisha, Arava, Singh, & Pariplavi, 2023). The pineal gland is mainly composed of the parenchyma formed by pinealocytes, connective tissue and glial tissue dominated by astrocytes (Lee, Ng, Lian, Yap, & Chuah, 2011). The surface of the pineal gland has the connective tissue capsule derived from leptomeninge differentiation, which extends into the pineal parenchyma with the blood vessels, dividing the parenchyma into many irregular lobular structures. The parenchyma of some pineal glands is arranged in an insular pattern, separated by more complex connective tissue (Gheban, Rosca, & Crisan, 2019).

Situated in the posterior part of the third ventricle, the pineal gland resides between the corpus callosum and the superior thalamus, uniquely positioned outside the blood-brain barrier, unlike most brain regions (Adams et al., 2017). It is connected to the brain by the pineal stalk and receives its blood supply from several arteries, including the posterior cerebral artery and the choroidal artery.

It has been reported that the pineal gland enlarges from birth up to 2 years of age and then stabilizes in size from age 2 to 20 years (Belay & Worku, 2023). There is also a correlation between pineal size and individual height and weight. Generally, individuals weighing between 61 and 70 kg have a relatively higher pineal gland density; while individuals with a height shorter than 165 cm have the smallest pineal width (Gheban et al., 2019).

The pineal gland, recognized as a neuroendocrine transducer, acts as a “circadian clock” regulating physiological and behavioral processes, converting neural signals from the suprachiasmatic nucleus of the hypothalamus into various hormones that play an important role in different organs (thyroid, neurohypophysis, etc.) (Harisha et al., 2023). The primary role of the pineal gland is the secretion
and release of melatonin, a hormone directly linked to light exposure and regulated by the circadian rhythm (Rosenstein, Estévez, & Cardinali, 1989). Light signals received by the retina are relayed via the hypothalamic bundle to the suprachiasmatic nucleus, inducing norepinephrine release, which binds and acts on β-adrenergic receptors in the pineal gland. The synthesis of melatonin subsequently modulated by increasing the activity of N-acetyl transferase (Patel et al., 2020), thereby influencing various physiological and behavioral processes.

Melatonin, or N-[2-(5-methoxy-1H-indol-3-yl) ethyl] acetamide, is a neurohormone widely considered to be involved in starting and maintaining sleep-wake cycles, blood pressure regulation, and seasonal reproduction (Esposito & Cuzzocrea, 2010). Due to the light dependence of melatonin synthesis, plasma concentrations of melatonin peak in the dark environment at night while remaining nearly undetectable during the day (Yang, Kim, Kim, & Cho, 2021).

The pineal gland is the main site for melatonin production. During the synthesis process, tryptophan, serving as the precursor of melatonin, first undergoes hydroxylation to 5-hydroxytryptophan within pinealocytes, which subsequently decarboxylated to serotonin under the catalysis of decarboxylase. Through the catalysis of acetyltransferase, serotonin transforms into N-acetyl-5-hydroxytryptamine by reaction with acetyl-CoA, and ultimately transforming into melatonin due to the action of methyltransferase (Gheban et al., 2019). With the progress of research, it has been found that the production of melatonin is not limited to the pineal gland. Other tissues including the retina, intestines, ovaries, testes, bone marrow, and lens also produce melatonin (Esposito & Cuzzocrea, 2010).

The melatonin produced by these tissues and organs mainly acts as a paracrine hormone, which means that melatonin produced by these organs primarily has a local effect, rather than being distributed throughout the body like the melatonin secreted by the pineal gland. Moreover, compared with the melatonin produced by the pineal gland, the functional significance of melatonin produced by other organs remains to be fully elucidated (Patel et al., 2020).

Furthermore, due to its biological regulatory function, the chemical synthesis process of melatonin has progressively matured. The amount of melatonin secretion is directly related to the volume of pineal gland parenchyma. However, an increase in the volume of pineal gland tissue does not necessarily imply an enhancement in pineal secretory activity. This is due to the fact that the increase in volume may derive from the proliferation of neuroglia and parenchymal calcification (Gheban et al., 2023), which can lead to a reduction in parenchyma volume, potentially impacting the number of pinealocytes and resulting in melatonin deficiency (Gorgulu & Koc, 2021; Junemann, Bukreeva, et al., 2023).

The main function of melatonin is to mediate circadian rhythms, while melatonin also assumes a pivotal role within the CNS, primarily through the activation of melatonin receptors (MTs) (Song, 2019). Substantial evidence underscores the diverse neurobiological effects of melatonin, including the enhancement of synaptic plasticity, facilitation of neurogenesis, and augmentation of memory function. Notably, melatonin can inhibit neuroinflammation, thereby contributing significantly to overall neural homeostasis (Esposito & Cuzzocrea, 2010).

Moreover, melatonin’s regulatory function plays a part in immune defense responses (Guerrero & Reiter, 2002). Studies indicate that immune cells are capable of synthesizing melatonin within the bloodstream, thereby regulating immune responses to stress conditions.

The initial discovery of melatonin’s powerful free radical scavenging properties was made three decades ago. Melatonin has been found to possess a potent anti-oxidant ability, allowing it to scavenge oxidative stress in various tissues (Novais, Chuffa, Zuccari, & Reiter, 2021), which has been proven to be independent of receptor-mediated actions. Beyond its direct free radical scavenging, melatonin is vital in oxidative defense, activating enzymes that convert free radicals and their products into harmless compounds (Tomas-Zapico & Coto-Montes, 2005). Moreover, melatonin is known to enhance the activity of key antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, at a molecular scale, emphasizing its role in enhancing the antioxidant defense system (Ghorbani, Pishkar, Saravi, & Chen, 2023).

The role of melatonin in cognitive function is evident, substantiating its positive impact on learning and memory. Melatonin supplements have demonstrated promising results as a therapeutic intervention, offering a potential avenue for addressing cognitive impairments. Extracellular vesicle (EV) melatonin therapy demonstrates significant potential in mitigating vascular calcification. Research indicates that
treating EVs isolated from Vascular Smooth Muscle Cells (VSMC) or calcified VSMC (CVSMC) with melatonin allows for their absorption by VSMCs, leading to the inhibition of osteogenic differentiation and senescence in both VSMCs and CVSMCs, thereby exhibiting therapeutic efficacy in a mouse model (Xu et al., 2020). Moreover, melatonin has been identified as a key player in attenuating vascular calcification by inhibiting mitochondrial fission through the AMPK/Drp1 signaling pathway. This highlights melatonin’s regulatory role in the cellular process associated with calcification (Chen et al., 2020). In summary, the utilization of extracellular vesicle melatonin therapy exhibits promising outcomes in alleviating vascular calcification by modulating relevant cellular processes. Additionally, the observed capacity of melatonin to mitigate vascular calcification implies its potential involvement in the Pineal gland calcification process.

In addition to secreting and releasing melatonin, recent research suggests that the pineal gland can exert inhibitory effects on the gonads, thereby regulating the reproductive system. Tan et al. (Tan et al., 2010) found that when photoperiodic mammals are pinealectomized, the yearly reproductive cycle is interrupted. Furthermore, the pineal gland, stimulated by darkness, is thought to modify the central regulation of pituitary gonadotrophin synthesis or release. The pineal gland has been associated with an inverse relationship between its size and the weight of the testis, as well as plasma and testicular testosterone levels, indicating its influence on gonadal physiology. Additionally, the pineal gland is implicated in influencing the neuroendocrine-thyroid axis, emphasizing its broader role in regulating endocrine functions beyond reproductive physiology.

3. PINEAL GLAND CALCIFICATION

Although the pineal gland, habenula and choroid plexus of the lateral ventricles are all common sites of intracranial physiological calcification, pineal gland exhibits the highest frequency of occurrence (Ghorbanlou, Moradi, & Mehdizadeh, 2022). Clinically, pineal gland calcification is a common physiological occurrence, with a prevalence that can be as high as 61.65% (Belay & Worku, 2023). It is generally acknowledged that pineal gland calcification is a process positively correlated with age. However, there are many children who have also been detected with pineal gland calcification, with the calcification rate approximating 2% in 5-year-old children, escalating to 35.8% in children aged 7 to 12. Astonishingly, the youngest child found with pineal gland calcification is mere 3 years old (Al Hajri, Sirasanangala, Boudaka, Al Dhuhi, & Al Ajmi, 2023). The calcification is potentially associated with the growth, development, and hormone levels of children, holding significant research value. Moreover, A few studies reported a correlation between pineal gland calcification and various neurological disorders, such as Alzheimer’s disease, schizophrenia, and Parkinson’s disease. This suggests that pineal gland calcification may play a role in the progression of neurological disorders, emphasizing the importance of investigating the functions and underlying mechanisms of pineal gland calcification. Pineal gland calcification is not limited to humans. According to research, pineal gland calcification is common in different species. An increasing number of animals, including ox, sheep, horses, donkeys, monkeys, cows, gerbils, rats, guinea pigs, chickens, and turkeys, have also been found to exhibit calcification of the pineal gland (Patel et al., 2020), providing a broad range of model choices for the study of pineal gland calcification and neurological disorders. Furthermore, calcification of the pineal gland may result in the formation of calculi akin to kidney stones.

3.1. Formation

The formation of pineal gland calculi has been attracted significant scientific interest, with studies suggesting that they predominantly form within the parenchyma, potentially originating from pinealocytes (Junemann, Bukreeva, et al., 2023). Concurrently, they are also present within the connective tissue septa. This has led to the hypothesis that calcification initially occurs in the pineal parenchyma, which is subsequently replaced by connective tissue. This has led to the hypothesis that calcification initially occurs in the pineal parenchyma, which is subsequently replaced by connective tissue (Junemann, Bukreeva, et al., 2023). Pinealocytes are characterized by the presence of vacuoles laden with flocculent and fibrous substances. Welsh (Welsh, 1984) and Krstic (Krstić & Golaz, 1977) have highlighted the pivotal role of vacuoles in the calcification process, proposing that calcium is transported into the vacuoles, leading to intracellular calcification. They hypothesized that the vacuole is the site of initial calcification in the cell. Furthermore, the cytoplasmic matrix, endoplasmic reticulum, and mitochondria are also considered potential initial sites of calcium deposition within pinealocytes, with formation of hydroxyapatite crystals.
As pinealocytes degenerate and die over time, the calculi diffuse into the extracellular space.

Understanding the mechanisms underlying pineal gland calcification is crucial due to its potential implications for various physiological and pathological processes. Pineal gland calcification is a complex process which may represent a physiological, maturation, or degenerative process, and its underlying causes remain elusive. Researchers have proposed several hypotheses on how these calculi form. Studies have shown a positive correlation between elevated fluoride levels in the human pineal gland and calcium accumulation (Mrvelj & Womble, 2020). Mrvelj and Womble found that eliminating fluoride from the diet promotes the proliferation of pinealocytes in elderly rats. Conversely, fluoride intake inhibits pineal growth (Gheban et al., 2021), leading to a decrease in melatonin. Fluoride is considered a beneficial substance for oral care, and the water supply in many countries has been fluoridated for a long time. Therefore, exploring the role of fluoride in pineal gland calcification and choroid plexus metastatic calcification has significant public health implications. Beyond that, mesenchymal stem cells have been proposed as potential contributors to the calcification process in the pineal gland. The high vascular supply of the pineal gland leads to elevated cytokine levels, attributed to chronic inflammation. This, in turn, promotes the proliferation and migration of mesenchymal stem cells, leading them to differentiate into osteoblasts and osteocytes through interactions with inflammatory mediators (Kopani et al., 2019). Additionally, the aggregation of hypertrophic cells in areas where calcium originates and deposits implies that these cells might also be involved in the calcification process (Whitehead, Oh, Raju, & Choudhri, 2015).

3.2. Various Types

Pineal gland calculi demonstrate a significant degree of heterogeneity, with variations in morphology, type, and composition observed across different individuals. These calculi, often round or elliptical, are typically several hundred micrometers in size (Junemann, Ivanova, et al., 2023), while aggregates can reach several millimeters. A substantial portion of these calculi exhibits a mulberry-like form and other large fractions consist of small, distinct crystalline cores (Bacconnier et al., 2002), which display a layered structure akin to compact bone (Bukreeva et al., 2023). This has led to theories proposing a similar mechanism of formation to that of bone calcification (Junemann, Bukreeva, et al., 2023). In some cases, dense particles have been identified at the center of calculi aggregates within the pineal gland, which can further develop into irregular or hollow structures. Interestingly, an increase in both the quantity and variety of pineal gland calculi has been observed with advancing age, with the emergence of concentric lamellar structures resembling growth rings. Research has suggested a correlation between the number of layers in these lamellar structures and the age of the individual, implying a relationship between the formation of concentric layers and periodic changes in pineal gland calcification levels (Harisha et al., 2023). Calculi found in the pineal gland of children differ from those found in adults. Typically, pineal gland calculi in children are punctate, with no observed aggregations of calculi (Whitehead et al., 2015). It remains unclear whether the calcification observed in pediatric cases is the result of a physiological process or indicative of potential pathology. Further research is warranted to elucidate the significance of pineal gland calcification in pediatric populations and its potential impact on neurodevelopment.

The composition of pineal gland calculi exhibits substantial variability. While hydroxyapatite is generally accepted as the primary component of pineal gland calculi, the presence of calcium carbonate crystals has also been documented. The clinical significance of these compositional differences remains unclear. There is an absence of organic matrix within the pineal gland calculi, while metallic elements such as magnesium, iron, copper, and zinc have been detected (Junemann, Ivanova, et al., 2023). Given the crucial roles these elements play within the human body, metallic element detection within the pineal gland could provide valuable insights into the mechanisms underlying the formation and pathological implications of pineal gland calculi.

3.3. Effects on Pineal Gland Function

The accumulation of calculi within the pineal gland can lead to hypoxia and subsequent pinealocyte death (Kopani et al., 2019). Moreover, hypoxia is known to cause an increase in vascular permeability and nitric oxide production in the pineal gland, which may contribute to the calcification process (Kaur, Sivakumar, Lu, & Ling, 2007). Pineal calcification can impact the production of melatonin, the most important hormone produced by the pineal
gland. The decrease of melatonin, in turn, promotes the calcification of pineal gland and thereby forming a cyclic exacerbation, which is associated with nerve diseases, such as schizophrenia.

3.4. Risk Factors

Numerous investigations have demonstrated a correlation between calcification of the pineal gland and various factors, including age, sex, altitude, sunlight exposure, race, nutritional changes, neurodegenerative diseases, unhealthy lifestyle habits, etc (Belay & Worku, 2023). Age is considered the primary risk factor for pineal gland calcification (Jalali et al., 2023).

A significant reduction in biosynthetic activity of the pineal gland has been observed in aging hamster (Reiter, Richardson, Johnson, Ferguson, & Dinh, 1980). The age-related decline in melatonin biosynthetic activity and the volume of the pineal parenchyma may be reflected in changes in the calcium homeostasis of pinealocytes, leading to age-related changes in pineal gland calculi. Histologically, it has been found that the number and size of pineal gland calculi increases with age from the fetal period to adulthood, exhibiting a structure similar to “growth rings”, accompanied by pineal degeneration. The rate of pineal gland calcification is only 40% in adolescents, but it rises to 70% after the age of 40, suggesting age-related alterations in pineal gland calculi.

The incidence of pineal gland calcification has been observed to be higher in males, with a prevalence rate is twice as high as in females (Jalali et al., 2023). This divergence between sexes may be attributed to specific lifestyle habits, such as smoking, which has been indicated as a contributing factor to vascular calcification in different tissues (Ozguner, Koyu, & Cesur, 2005). Moreover, Jalali (Jalali et al., 2023) have proposed smoking affects melatonin levels and a notable correlation exists between smoking and elevated levels of pineal gland calcification in individuals aged 63 and above. However, whether smoking can induce pineal gland calcification through a similar mechanism that induces calcification of VSMC remains to be further investigated.

The prevalence of pineal gland calcification exhibits geographical variations, with calcification rates ranging between 35.2% and 76% across various nations (Belay & Worku, 2023). This variation in calcification prevalence may be influenced by environmental factors. Light is the most typical environmental factor. It has been suggested that individuals living in low-altitude areas and those with low intensity of sunlight exposure are more prone to pineal gland calcification. This susceptibility may be attributed to sunlight as a major source of vitamin D, which plays a crucial role in regulating calcium metabolism (Razzaque, 2011).

The influence of ethnicity on the prevalence of pineal gland calcification has also been explored. The prevalence of pineal gland calcification has been consistently observed to be higher in individuals of white ethnicity compared to other ethnic backgrounds. This difference in prevalence has been attributed to genetic factors or variations in lifestyle and environmental factors across different ethnic groups (Jalali et al., 2023).

In addition to age, gender, smoking, sunlight exposure, and ethnicity, other risk factors for pineal gland calcification have been investigated. A sedentary lifestyle, obesity, and certain medical conditions, such as hypertension and diabetes, have been linked to a heightened risk of calcification.

3.5. Diagnosis

Cerebral computed tomography (CT), Magnetic Resonance Imaging (MRI) and Immunohistochemistry (IHC) represent valuable methods for both diagnostic and research of pineal gland calcification. CT plays a pivotal role in the identification of intracranial calcification. During CT examinations, intracranial calcification manifests as high-density shadows. MRI provides a non-invasive means for visualizing the pineal gland, facilitating the comprehensive evaluation of its volume and morphological characteristics. This imaging modality has been employed to establish correlations between pineal gland volume and melatonin levels, contributing valuable insights into the physiological implications of calcification process (Sigurdardottir et al., 2016). IHC serves as a pivotal technique in the histological analysis of the pineal gland. This methodological approach enables the precise identification of specific proteins and markers associated with the intricate process of calcification. By elucidating the molecular underpinnings of calcification, IHC contributes to a nuanced understanding of the cellular and molecular events that underlie pineal gland calcification, thereby enriching diagnostic capabilities and advancing research endeavors in this domain.
4. POTENTIAL LINKS BETWEEN PINEAL GLAND CALCIFICATION AND CENTRAL NERVOUS SYSTEM DISEASE

4.1 Alzheimer’s Disease (AD)

CT scans reveal more distinctive characteristics of pineal gland calculi in AD patients. Within pathological samples of AD, calculi within severely degenerated parenchyma exhibit more hollow or concentric structures or display large and deep fissures (Bukreeva et al., 2023). AD is a widespread neurodegenerative condition characterized by a decline in cognitive functions and the onset of memory impairment. The two main pathological features of AD are the formation of neurofibrillary tangles, which are aggregates of hyperphosphorylated tau protein, and the accumulation of beta-amyloid plaques in the brain. These pathological changes lead to the progressive degeneration of neurons and subsequent cognitive impairment in patients. The clinical manifestations of AD include progressive memory loss, decline in cognitive function, and disturbances in sleep patterns. As a prevalent contributor to dementia among the elderly population, AD presents a substantial challenge for individuals, families, and healthcare systems globally. It is estimated that there are currently over 50 million people living with AD globally, and this number is expected to increase as the population aging. By 2050, it is projected that the number of individuals with AD will reach 150 million, placing a substantial strain on society and healthcare resources. The pathogenesis of AD is multifactorial and complex, involving interactions between genetic, environmental, and lifestyle factors. Comprehending the intricate interaction between genetic and environmental factors in the development of AD is essential for devising successful prevention and treatment approaches, aiming to alleviate the increasing impact of AD on society.

Patients with AD exhibit sleep disturbances from the early stages, making it an important diagnostic indicator for predicting the progression of AD. AD models are characterized by Aβ deposition, and a relationship exists between the extent of sleep quality disruption and cognitive dysfunction (Lim, Gerstner, & Holtzman, 2014). Researcher has indicated a link between reduced sleep duration and lower sleep quality in the elderly, correlating with increased Aβ deposition, further emphasizing the association between sleep disturbances and AD progression (Gao et al., 2020). Additionally, sleep disturbances have been shown to intensify microglial reactivity and promote Aβ deposition in a manner dependent on TREM-2, highlighting the intricate connection among sleep, neuroinflammation, and the pathology of AD (Parhizkar et al., 2023).

The pineal gland produces melatonin, a vital factor in the regulation of sleep. Therefore, the role of the pineal gland in AD pathology has been the focus of extensive research. Reduced melatonin in both serum and cerebrospinal fluid has been observed in AD patients compared to healthy individuals, which is associated with cognitive impairment, underscoring the potential impact of pineal gland dysfunction on AD pathogenesis (Song, 2019).

Aβ is one of the most critical indicators in the pathological processes of AD and represents a potential therapeutic target. Melatonin plays a crucial role in regulating and clearing Aβ deposition. ADAM10 and BACE1 are key enzymes in the non-amyloidogenic and amyloidogenic pathways, respectively, with the latter leading to excessive Aβ generation and ultimately contributing to AD pathology. Melatonin can modulate ADAM10 and BACE1 through pathways such as JAK2/STAT1 and PI3K/Akt, promoting α-secretase activity while inhibiting β-secretase function, thereby suppressing Aβ production. Additionally, melatonin can directly interfere with amyloid precursor protein expression via cAMP. Not only does melatonin regulate Aβ generation, but it also inhibits Aβ aggregation by directly interacting with it and participates in the clearance process in AD pathology (Li, Zhang, Wan, Liu, & Sun, 2020). These findings highlight the significant clinical therapeutic potential of melatonin in the pathological processes of AD.

In a transgenic rat model of AD, continuous use of melatonin for two months can promote the growth of hippocampal synapses, reduce Aβ accumulation in the cortex and hippocampus by 37% and 43% respectively, prevent mitochondrial dysfunction, and reduce degenerative changes in tissues (Alghamdi, 2018). Compared with the rats that orally received melatonin, rats injected only with soluble Aβ42 in the lateral ventricle without melatonin treatment exhibited an increased number of hippocampal astrocytes, along with prominent functional disorders and poorer spatial memory abilities (Liu et al., 2013). In clinical practice, the administration of melatonin supplements prior to sleep to enhance sleep quality and cognitive performance to a certain degree.

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Ozansoy et al. established an in vitro Aβ toxicity model, demonstrating that melatonin can inhibit Aβ toxicity by blocking the secretion of EV molecules, thereby influencing the levels of Tau protein carried by exosomes (Ozansoy et al., 2020).

Elevation in the pro-inflammatory cytokine tumor necrosis factor (TNF) serves as a biomarker indicating the advancement of AD, and melatonin can inhibit its expression, reducing neuroinflammatory responses (Zhang et al., 2019). Additionally, melatonin has demonstrated anti-inflammatory effects by suppressing the expression of the NLRP3 and the activation of NF-κB, while up-regulating the expression of the transcription factor Nrf2 (Muñoz-Jurado et al., 2022).

Pineal gland calcification is directly associated with a reduction in melatonin release. The degeneration of calcified pineal parenchyma contributes to a decrease in the number of pinealocytes that secrete melatonin. So far, although there are contrary conclusions, the mainstream theory believes that pineal gland calcification in AD patients is more severe and the volume of the pineal gland is smaller. These inconsistent findings may arise from individual and regional variations in the pineal gland and the current limitations in research techniques (Bukreeva et al., 2023).

4.2. Schizophrenia

Melatonin, as a therapeutic agent for schizophrenia, has demonstrated positive effects, suggesting that pineal gland damage and calcification may be implicated in the regulation of schizophrenia progression. Schizophrenia is a profound mental disorder marked by symptoms like disordered thinking, hallucinations, and delusions. Individuals diagnosed with schizophrenia frequently experience emotional dysregulation and deficits in social cognitive functioning. Moreover, they may exhibit disturbances in the attribution of thoughts and sensations, perceiving them as external rather than originating from within themselves. The etiology of schizophrenia is multifaceted, involving both genetic and environmental factors. Drug abuse, inadequate nutritional intake during gestation, and childhood adversity are risk factors for schizophrenia (Howes & Murray, 2014; Koenig, Kirkpatrick, & Lee, 2002). Dysregulation in certain neurotransmitter, disruptions in clock genes, activation of oxidative and immune-inflammatory, and structural abnormalities in the brain also seem to contribute to the pathophysiology of the disease (Kamath, Virdi, & Winokur, 2015). An estimated 24 million individuals worldwide are impacted by schizophrenia worldwide, with approximately half of these patients affected for life. Schizophrenia is often associated with unemployment, and homelessness, leading to a range of societal issues. While the pathological mechanism of schizophrenia remains unclear, increasing evidence suggests a correlation with pineal gland dysfunction (Sandyk, 1992).

Circadian rhythm disruptions are common in patients with schizophrenia, leading to sleep disorders, lack of energy, and declines in attention and memory, imposing a heavy burden on patients. Based on the research, it is evident that patients with schizophrenia experiencing disruptions in circadian rhythm show a correlation with reduced melatonin production. Supplementary melatonin has been investigated as a potential adjunctive treatment for schizophrenia, showing promise in improving sleep parameters, and counteracting metabolic adverse reactions and tardive dyskinesia symptoms caused by antipsychotic drugs (Duan, Jenkins, & Castle, 2021). Furthermore, melatonin is advantageous due to its low cost, minimal side effects, lack of drug interactions, and easy availability (Moon, Kim, Partonen, & Linnaranta, 2022). Imaging studies have revealed that patients with schizophrenia exhibit more severe pineal gland calcification and smaller parenchymal volume, suggesting a potential link between pineal gland calcification and the regulation of schizophrenia by melatonin (Takahashi et al., 2021).

4.3. Parkinson’s Disease (PD)

PD is a chronic and progressive neurodegenerative disorder characterized by symptoms such as dyskinesia, tremors, muscle rigidity, and speech difficulties, often associated with depression and sleep disturbances. Currently, the prevailing consensus is that PD primarily stems from a gradual and progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), coupled with a reduction in dopamine (DA) levels in the striatum (Surmeier, 2018). PD represents a severe neurological disease highly correlated with the aging process. According to 2019 statistical data, there are over 8.5 million patients globally, and the figure is expected to rise continuously with the ongoing aging of the population. Statistically, approximately 90% of PD patients manifest sleep disturbances. PD patients can experience a variety of sleep-related symptoms, such as increased REM sleep, reduced slow-wave sleep, and insomnia. These sleep disturbances can significantly impair daily functioning and quality of life.
disturbances, coupled with disruptions in circadian rhythm and cognitive decline (Macías-García et al., 2022). Additionally, sleep disturbances in PD have been associated with modifications in both melatonin secretion levels and the expression of melatonin receptors MTs within the SNc, suggesting a possible involvement of the pineal gland and melatonin in the progression of PD (Noseda et al., 2021).

Melatonin has been extensively studied for its therapeutic effects in the 6-OHDA-induced dopaminergic neurodegeneration model of PD (Sharma, McMillan, Tenn, & Niles, 2006), primarily attributed to its neuroprotective effects related to antioxidant activity, including free radical scavenging, decreased levels of lipid peroxidation, along with the alleviation of oxidative damage to mitochondrial DNA (Mack et al., 2016).

The brain-derived neurotrophic factor (BDNF) plays a pivotal role in the development and maintenance of dopaminergic neurons, and its expression is hindered in the progression of PD. Research has found that mRNA and protein levels of BDNF are elevated after melatonin treatment in the cortex and hippocampus of rats, which are accompanied by sleep disturbances induced by PD (Scalzo et al., 2010). Clinical administration of melatonin to patients with PD has also demonstrated a partial restoration of BDNF expression.

These examples illustrate that melatonin exerts neuroprotective and antioxidant effects in the PD model, offering potential reparative effects to attenuate dopaminergic neuron damage and disease progression.

Patients with PD have been observed to show notably reduced melatonin levels, potentially linked to pineal gland degeneration (Breen et al., 2014). Additionally, dysregulation of calcium ion influx in PD patients, associated with disrupted calcium signaling pathways, may also contribute to neuronal damage and death (Zündorf & Reiser, 2011). These findings suggest a potential association between PD pathogenesis and pineal gland calcification.

### 4.4. Other central nervous system diseases

The calcification of the pineal gland exerts a widespread impact on the homeostasis of the central nervous system. In comparison to healthy individuals, patients with depression (Zhao et al., 2019), stroke, and multiple sclerosis exhibit a significant decrease in melatonin levels, concomitant with pineal gland calcification. Further analysis of patient cohorts reveals that pineal gland calcification serves as a risk factor for stroke, with a 1.35-fold increased risk when pineal gland calcification is present (Kit-khuandee, Sawanyawisuth, Johns, Kanpittaya, & Johns, 2014). In the study of multiple sclerosis, the degree of fatigue in patients is also associated with pineal gland calcification.

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**Table 1.** The Role of Pineal Gland Calcification in AD, Schizophrenia, and PD.
5. CONCLUSION

In this review, we delve into the discussion on pineal gland calcification and its significance in CNS diseases, with a specific focus on its roles in AD, schizophrenia and PD (Table 1). Our aim is to propose the potential impact of pineal gland calcification on neurological health.

We suggest pineal gland calcification as a dynamic process characterized by the formation and breakdown of calcified regions, exhibiting heterogeneity within different individuals and even within the same individual. Pineal gland calcification is a complex phenomenon with regional variations, and its underlying mechanisms remain unclear at present.

Currently, it is accepted that the pineal gland, by secreting and releasing melatonin, plays a role in reducing individual immune inflammatory responses and promoting the anti-oxidative process, thereby influencing the onset of AD, schizophrenia and PD. Pineal gland calcification disrupts this process, affecting the secretion and release of melatonin, consequently leading to central nervous system imbalance.

So far, pineal gland calcification is considered a physiological process. However, considering the relationship between pineal gland calcification and various neurological disorders, it is valuable to explore the potential impact of pineal gland calcification on basic medical and clinical practice.

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Conflict of Interest Disclosures

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List of abbreviations

CNS central nervous system
MTs melatonin receptors

EV extracellular vesicle
VSMC vascular smooth muscle cells
CVSMC calcified vascular smooth muscle cells
CT computed tomography
MRI Magnetic Resonance Imaging
IHC Immunohistochemistry
AD Alzheimer’s Disease
TNF tumor necrosis factor
PD Parkinson’s Disease
SNC substantia nigra pars compacta
DA dopamine
BDNF brain-derived neurotrophic factor

REFERENCES


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