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Recent descriptions on physiological concepts of the pineal gland: what's new?

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ABSTRACT

The pineal gland is an endocrine organ located in the cranial vault. Its endocrine function has been extensively studied and has been found to be the cause of important regulatory functions in the physiology of the human body. Although the initial approaches to the suggestive action of this organ on the organism were of a philosophical and spiritual nature, in the last century technological advances have made it possible to clearly elucidate its effector function as an endocrine gland. In this order of ideas, the objective of this review is to address basic and recent descriptions of the physiology of the pineal gland.

Keywords
pineal gland,
endocrine system,
melatonin,
central nervous system,
physiology

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Introduction

The pineal gland (PG) has been described as an organ that is capable of excreting a hormone called melatonin (MLT) that plays an important role in the circadian cycle (1). At the beginning of mankind's interest in anatomy and physiology (Renaissance era) this gland was still considered as part of the spiritual component of the body, as science evolved through later discoveries that the pineal gland exerted a regulating and synchronizing effect on the physiology of the organism, it was given physical functions (2). The scope of the hormone it excretes extends to important fields of human physiology such as the circadian cycle, sleep-wake cycle, mood states (its deficit causes depressive states), some topics that we will go into below, but not before addressing what was assumed about this gland throughout history.

History

The PG has been the subject of debate in philosophical circles. It was Ariens-Kappers who expressed that the oldest references with physiological-spiritual connotations regarding this gland were made by Herophilus, a philosopher who proposed that the PG had control over blood circulation by functioning as a sphincter that regulated the flow of *pneuma psychikon*, or the breath of life, from the central ventricle to the posterior ventricle in the brain (3). Galen proposed that the PG was nothing more than a pseudo-lymphatic gland that functioned as an anchor site to the intricate network of blood vessels that irrigate the brain mass belonging to the dorsal and posterior diencephalon regions, a somewhat more physical approach, however, still related to spiritual theories (4).

In the Middle Ages, different theories enriched the *theoretical corpus* regarding the duality between the soul and the body, assigning to the organs some probable spiritual functions, with new thoughts or improvement of the existing ones by important figures such as Thomas Aquinas, a famous monk influenced by the prevailing Christianity of the feudal age (5). In the Renaissance there was an explosion in anatomical explorations led by important figures such as Leonardo Da Vinci, who through his detailed drawings of human anatomy deepened the curiosity of the medical eminences of the time about the vital functions of different organs (6). The soul was located in the third ventricle of the brain, while the spinal cord was responsible for distributing the sensations generated in the soul to the body (6). Later Descartes proposed that the soul should have a physical residence or physical counterpart in the human body, the PG being the abode of the soul. According to him, the cerebral organs were duplicated except for the PG, which was curiously located in the center of the brain (7). Descartes' theories were later discredited by figures such as Antoine Jacques Louis Jourdan who argued that his ideas were nothing more than chimeras relegated to the realm of fiction (8).

Descartes' theories were later discredited by figures such as Antoine Jacques Louis Jourdan who argued that his ideas were nothing more than chimeras relegated to the realm of fiction (9). In addition, it was also hypothesized that the pineal is an endocrine gland. In 1958, it was determined that the pineal gland secretes melatonin, which regulates the circadian rhythm in the studies of Lerner et al (1,10). The history of the pineal gland is long and its functions were only elucidated in the 20th century. In previous centuries the gland's functions were based on superstition and a misunderstanding of its anatomy. However, even with our better understanding of the gland, all of its functions have yet to be determined (11).

Embryology and histology

The PG is formed from the neuroectoderm of the posterior portion of the roof of the diencephalon. It is initially recognized in the caudal portion of the diencephalon as a structure called the pineal body. This pineal body is nothing more than an epithelial thickening in the midline at the level of the diencephalon that from the seventh week begins to undergo a process of invagination that will culminate in the formation of the solid organ (12).

Histologically the PG is mainly composed of two types of parenchymal cells. Pinealocytes and interstitial cells (13). Pinealocytes are organized in lobules formed by connective tissue. They are mainly characterized by the production of MLT, a hormone important for metabolic regulation processes, as well as for the control of the sleep-wake cycle (14). Interstitial cells constitute approximately 5% of the cell types in this gland, established as supporting cells in the tissue (15).

Morphological structure

The PG has been described as a small, odd, endocrine organ located in the roof of the midbrain, above the superior colliculi and behind the third ventricle (16). It is joined to the habenular and posterior commissures by means of the pineal stalk, whose body is bathed by cerebrospinal fluid and covered by pia mater, the pia mater in turn becomes a capsule that provides the gland with partitions that in turn allow its irrigation (17). The so-called pineal region, however, contains the gland in a wider space, defined by the corpus callosum and the choroid plexus of the third ventricle above, by the lamina quadrigemina and the cerebellum below, and laterally by the thalamus and the cerebral hemispheres (18).

The weight of the gland can vary between 100 to 200 mg, and measure between 5 to 8 mm long and 3 to 5 mm wide (12). Its innervation is given mainly by the superior cervical ganglion of the paravertebral chain, of sympathetic and parasympathetic type (12,13).

On the other hand, its irrigation, unlike others in the body, is considered of a high flow considering that it is a small endocrine organ, in addition to the fact that the blood vessels that integrate it lack a blood-brain barrier (13,16). In addition, a study by Macchi & Bruce identified that the PG reached a blood flow that equaled the neurohypophysis in rats and was exceeded only by the flow from the kidneys (12,13). Cellularly, it has been described that pinealocytes, so called the cells that compose the PG, are equivalent to those found in the retina, more specifically to retinal cones, lower order neurons and glial cells; therefore, it was mainly catalogued as a visual organ (12).

Neurological pathways and tracts

Anatomically, the structures that make up the central nervous system comprise a series of complex interconnected pathways for the fulfillment of various functions (15). The PG communicates via the suprachiasmatic nucleus (SCN) and the retinohypothalamic tract (RHT), such that afferent fibers coming from the RHT are mainly located in the ventrolateral region of the CNS, while efferents depart to the dorsolateral region (15).

The most studied afferent pathway is part of the visual pathway, starting in the ganglion cells of the retina, which are conducted through the optic nerve and optic chiasm until they reach the hypothalamus, however, it is independently of the perception of images (12,15).

On the other hand, the efferent fibers that cross the suprachiasmatic nucleus form the so-called multisynaptic pathway of the PG, whose route guides it to the hypothalamus, specifically its paraventricular nucleus, from there its axons depart to preganglionic neurons in the lateral intermediate column of the sympathetic type in the spinal cord between the T1 and T3 segments, and to the superior cervical ganglion where they activate noradrenergic neurons (18). The latter form the *nervus conarii*, whose fibers reach both sides of the tentorium and unite in the midline to finally enter the PG in its posterior portion, taking the name of pineal nerve (13,18). The parasympathetic innervation is provided by the sphenopalatine nerve and the otic ganglia. And for its part, the trigeminal ganglion through some of its branches also provides innervation to the gland (14).

Neuroendocrine component

The main hormonal molecule secreted by the PG is MLT, which is able to exert many endocrine functions at the CNS level and throughout the body physiology, so it is not considered a pure neural hormone (19). MLT is an endogenous indolamine, with circadian regulation given by the suprachiasmatic nucleus; characteristically, it is a lipophilic hormone, which confers it the ability to rapidly cross the blood-brain barrier and target cells of its action (20).

MLT is released into the bloodstream, following the endogenous circadian cycle given by the hypothalamus, through the light-dark cycle, i.e. it is produced during the night as long as it is dark, in addition to the sympathetic stimulation given by the adrenergic nerves that make up the hypothalamic retino pathway (18,21). Because melanopsin decomposition is stimulated during the day in the retinal ganglion cells, it uses the hypothalamic retinal pathway to carry its signal to the hypothalamus and thus inhibit its synthesis. It is synthesized from an essential amino acid, tryptophan, which is biotransformed by the action of four enzymes (20).

Initially, tryptophan through the action of the enzyme tryptophan hydroxylase, which adds a hydroxyl group to the 5-position of the indole ring to form 5-hydroxytryptophan (5-HTP). Subsequently, 5-hydroxytryptophan forms serotonin via an aromatic

amino acid decarboxylase. Now, before finally being MLT, serotonin is transformed by the enzyme serotonin N-acetyltransferase. And finally, MLT is formed from N-acetyl serotonin as substrate and obligatory step for its synthesis by means of the enzyme hydroxyindole-O-methyltransferase (20-22).

After its synthesis, MLT travels through the bloodstream bound to albumin, and upon reaching the liver it is metabolized to 6-hydroxymelatonin by cytochrome P450, mainly in its CYP1A2 isoform, and the latter is conjugated to 6-sulfamethoxymelatonin for its subsequent urinary excretion (21).

Regulation and functions of the pineal gland

It has been difficult to determine all the physiological functions of PG because its main product (MLT) has a complex regulation in vivo, being controlled by various stimuli inside and outside the individual. Therefore, experimental studies have not found a way to reproduce the exact pattern of natural MLT production (22-24), but we know that the main regulation comes from the suprachiasmatic nucleus, which is the circadian pacemaker (20,23,24).

MLT peaks depend on light exposure and season (due to changes in day length). MLT production increases in the dark phases of the day in almost all animals. Light exposure in the retina stimulates the suprachiasmatic nucleus which sends signals that decrease MLT production. This regulation gives the body representation of external environmental conditions (28-31).

Other factors involved in MLT production are adrenergic stimuli and inflammatory products. Another important source of control is known to be the release of noradrenaline (NE) by the sympathetic fibers of the cervical sympathetic ganglia that stimulate its secretion mainly at night (24,30,31,32,33). Extra-pineal MLT production is also under the control of several neurotransmitters (glutamate, acetylcholine, vasoactive intestinal peptide, substance P and pituitary adenylate cyclase-activating peptide), but to a lesser extent than NE (27,30). Inflammatory products can increase or decrease MLT production. Pathogen- and hazard-associated molecular patterns (PAMP and DAMP) modulate nocturnal MLT synthesis during inflammatory processes (27,33). In addition, several cytokines and signaling pathways such as IFN, LPS, beta-amyloid peptide, NFκB, JAK/STAT have been observed to have complex effects on MLT production (33).

MLT has a wide range of effects in the body and acts through two G-paired protein receptors (MT1, MT2) and another of the quinone reductase family: MT3 (27). It is involved in important and basic processes in mammalian life, such as the timing of seasonal physiology, reproduction and sleep **(Table 1).**

Table 1. Summary of pineal gland functions (21,24,31).

- Negative regulation of thyroid activity
- Hypothermic
- Sleep inducer
- Hypotensive by increasing norepinephrine levels, regulating cardiac beta receptors and increasing mesenteric arterial dilation capacity
- Immunoregulatory through the use of transcription factor NFκB and binding to κB receptors, regulating glucocorticoid and MLT synthesis rates
- Antioxidant by inducing the Nrf2-ARE signaling pathway and scavenging free radicals
- Oncostatic
- Thymic modulator
- Neuroprotector

Reproduction

PG has several effects on reproduction and sexual maturation due to its effects on the regulation of hormone release at the pituitary level. It determines gametogenesis, sexual maturation, pregnancy and menopause (35). It is considered to have paradoxical effects at the reproductive level as its effect depends on peaks of secretion and the season in which it occurs. However, it is not yet clear how the duration of MLT exposure in the *pars tuberalis* may affect TSH and GnRH release and its effects on peripheral tissues to regulate reproduction (22,24).

Sleep

Park et al investigated the relationship between pineal gland volume (PGV) and symptoms of REM sleep behavior disorder (RBD) in a cohort of previously healthy individuals. They followed the cohort for two years and administered the REM Behavioral Sleep Disorder Screening Questionnaire (RBDSQ) and measured VMP by magnetic resonance imaging (MRI). The results showed that individuals with symptoms or at risk for RBD had a smaller PGV (37). This finding is supported by other studies, just

as PG calcification and cysts are also known to trigger sleep disturbances (27). MLT deficits due to weight gain and obesity have deleterious effects on sleep, circadian rhythm, and neuroendocrine functions (30,37). In addition, it has been shown in several studies that MLT administration greatly improves sleep disorders (34,37,38).

MLT improves sleep through several mechanisms by acting on muscle tone, controlling GABAergic function and improving sleep efficiency (33).

Circadian rhythm

In mammals, PG adjusts organisms to respond to the needs of each season and choose the best time of the year for reproduction, hibernation, etc. as it translates environmental changes depending on changes in light during the day. MLT acts on clock neurons and clock genes to generate a circadian rhythm (33,34).

It appears that gestational MLT synchronizes maternal and fetal circadian clocks and also regulates the timing of offspring puberty, as it also determines fetal adrenal development (23,30). Nowadays the circadian rhythm can be altered due to exposure to nocturnal light. This alteration may even increase the likelihood of tumor growth as the protective effect of MLT is lost (23).

Mood

PGV is associated with mood disorders (39). There have been reports of abnormal MLT secretion and increased expression of stress hormones at night that alter sleep and, consequently, mood. It has a relationship not only with mood disorders, but also with other mental illnesses such as schizophrenia (26).

In depression, MLT has been used as a treatment because its levels decrease during the crisis and increase immediately after recovery (25).

Pregnancy

During pregnancy, MLT is responsible for synchronizing maternal and fetal physiology and guiding fetal development through MLT receptors in the fetal pituitary gland. In addition, the circadian rhythm of maternal control by light exposure and transmitted to the fetus as an MLT signal determines the future behavior of the offspring in terms of growth and sexual maturation (28). On the other hand, MLT levels in lactation show no relationship with offspring behavior and circadian regulation (23).

Temperature

The relationship between MLT and core body temperature is still a matter of debate. Some research shows a decrease in MLT during the rise in temperature in the ovulatory phase of the menstrual cycle and a higher peak MLT concentration during the luteal phase than during the follicular phase (35).

Endocrine control

In a case-control study, the PGV was compared with MRI techniques. It showed that healthy controls had a larger PGV in contrast to obese people. And that PGV was inversely related to body mass index (BMI). Decreased LTM has also been related to insulin resistance and the presence of type II diabetes mellitus (37).

Pain

MLT has an effect on pain control through its effects on sleep, and control over neurotransmitters such as GABA and dopamine. It can decrease cyclic AMP production and activates the opioid receptor directly or indirectly. In addition, in animal models, a decrease in NMDA-induced currents in spinal cord gelatinous neurons has been observed (38).

Oxidative Stress

MLT protects the cell through its direct and indirect antioxidant and anti-inflammatory effects, as it is a neutralizer of oxygen free radicals, as well as regulating the activation of second messengers that activate pro-inflammatory pathways such as cAMP and cGMP. It has been shown that it can control transcription factors related to the retinoic acid receptor (ROR) (27,30). It has also been shown to have protective effects on X-ray exposure (24).

Neurogenesis

MLT also plays a neuroprotective role in many central nervous system disorders, especially in dementias. MLT is thought to exert anti-neurodegenerative properties through ROR receptors (30) and the disappearance of MLT receptors leads to neuropsychiatric disorders in the elderly (25).

In Alzheimer's disease (AD) it has been identified that MLT production is impaired and leads to

impaired neurogenesis due to reduced expression of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor. MLT stimulates neural stem cell replication in the midbrain and hippocampus, depending on day length (27).

Other functions

The effects of MLT are not only central. In the gastrointestinal tract, MLT has protective effects on the gastric mucosa. In addition, it has regulatory effects on the immune response that controls leukocyte migration, inhibits the activation of inflammatory signaling, and regulates the proliferation and activation of immunocompetent cells (24). It also has regenerative effects on corneal lesions and regulation of intracranial pressure (24).

There is evidence that reduced levels of MLT contribute to cognitive impairment in AD patients. This not only affects cognition but also sleep and circadian rhythm (27). In addition, MLT appears to be involved in the pathogenesis of AD, as it is implicated in the inhibition of tau phosphorylation, attenuated levels of beta-amyloid protein precursor production and its deposition in the CNS (27).

Melatonin could be considered a cardioprotective agent, it is associated with a reduction of iatrogenic lipoproteins (40). In a murine model, hypercholesterolemia was induced in rats by a diet rich in lipids and carbohydrates, melatonin was administered orally at a dose of 10 mg/kg/day, presenting in the lipid profiles measured. Subsequently, these profiles were characteristically antiatherogenic: total cholesterol, very low-density lipoprotein (VLDL) and low density lipoprotein (LDL) concentrations decreased, while high density lipoprotein (HDL) cholesterol concentrations increased (41). Another product of PG (and other peripheral tissues), N-dimethyltryptamine, is responsible for perception, consciousness, vision, imagination and dreams, and has potential therapeutic targets for depression, anxiety and psychosis (24).

Future perspectives include the need to investigate whether there are chronic changes in the physiology of the pineal gland due to the new disease called COVID-19, specifically due to the neurotropism of SARS-Cov-2 and neuroinflammatory mechanisms caused by this virus (42-45). In addition, the development of robotic neurosurgery and other emerging techniques such as neurogenomics and neuroimaging genetics should also be encouraged in order to better understand the pathophysiology of pineal gland-associated diseases (46,47).

Conclusions

The pineal gland is an endocrine organ that fulfills multiple functions in the physiology of the body, so it is very important to understand and study it. Its main product is the hormone melatonin, in future research this hormone could play a major role in the therapy of multiple neurodegenerative pathologies, such as Alzheimer's disease, schizophrenia and major depressive state, as well as protector of heart and cerebrovascular diseases.

References

1. Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W. Isolation of melatonin, the pineal gland factor that lightens melanocytes 1. J Am Chem Soc. 1958; 80(10):2587–2587.
2. Arendt J. Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology. Rev Reprod. 1998; 3(1):13–22.
3. Ariëns-Kappers J, Pévet P. Short history of pineal discovery and research. Amsterdam - New York: Elsevier; 1979. 1–22.
4. Zrenner C. Early theories of pineal functions. Pineal Res Rev. 1985; 3:1–40.
5. Smith CUM. Descartes' Visit to the Town Library, or how Augustinian is Descartes' Neurophysiology? J Hist Neurosci. 1998; 7(2):93–100.
6. Brazier M. A history of neurophysiology in the 17th and 18th centuries: From concept to experiment. By Mary. A. B. Brazier New York, Raven Press, 1984. 239.
7. López-Muñoz F, Boya J. The role of the pineal gland in Cartesian psychophysiological doctrine. Acta Physiol Pharmacol latinoam. 1992; 42:205–16.
8. Jourdan AJL. Dictionnaire des sciences médicales. Paris; 1820.
9. Zrenner C. Theories of pineal function from classical antiquity to 1900: a history. Pineal Res Rev. 1985; 3:1–40.
10. Lerner AB, Lerner MR. Congenital and hereditary disturbances of pigmentation. Bibl Paediatr. 1958; 14:308–313.
11. Shoja MM, Hoepfner LD, Agutter PS, Singh R, Tubbs RS. History of the pineal gland. Child's Nerv Syst. 2016; 32(4):583-586.
12. Sadler TW, Langman J. Langman's medical embyology. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2019.
13. Ross MH, Pawlina W. Histology: a text and atlas: with correlated cell and molecular biology. Seventh edition, International edition. Philadelphia: Wolters Kluwer; 2016.
14. Sahai A, Sahai RK. Pineal gland: A structural and

functional enigma. J Anat Soc India. 2013; 62(2):170–7.
15. Roa I, del Sol M. Pineal Gland Morphology: A Literature Review. Int J Morphol. 2014; 32(2):515–21.
16. Granados AM, Ospina C, Paredes S. Pineal gliosarcoma in a 5-year-old girl. Radiol Case Reports. 2018; 13(1):244–7.
17. Yelamanchi SD, Kumar M, Madugundu AK, Gopalakrishnan L, Dey G, Chavan S, et al. Characterization of human pineal gland proteome. Mol Biosyst. 2016; 12(12):3622–32.
18. Guadarrama-Ortiz P, Ramírez-Aguilar R, Madrid-Sánchez A, Castillo-Rangel C, Carrasco-Alcántara D, Aguilar-Roblero R. Controladores del Tiempo y el Envejecimiento: Núcleo Supraquiasmático y Glándula Pineal. Int J Morphol. 2014; 32(2):409–14.
19. Hull JT, Czeisler CA, Lockley SW. Suppression of Melatonin Secretion in Totally Visually Blind People by Ocular Exposure to White Light. Ophthalmology. 2018; 125(8):1160–71.
20. Chen Y, Tain Y, Sheen J, Huang L. Melatonin utility in neonates and children. J Formos Med Assoc. 2012; 111(2):57–66.
21. Amaral FG do, Cipolla-Neto J. A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab. 2018; 62(4):472–9.
22. Abou-Easa K, El-Magd MA, Tousson E, Hassanin A, Shukry M, Salama M. Pineal Gland Plays a Role in Gonadal Development after Eyelids Separation in Puppies. Int J Morphol. 2015; 33(1):7–18.
23. Gorman MR. Temporal organization of pineal melatonin signaling in mammals. Mol Cell Endocrinol. 2020; 503:110687.
24. Gheban BA, Rosca IA, Crisan M. The morphological and functional characteristics of the pineal gland. Med Pharm Reports. 2019; 92(3):226–34.
25. Zhao W, Zhu D, Zhang Y, Zhang C, Wang Y, Yang Y, et al. Pineal gland abnormality in major depressive disorder. Psychiatry Res Neuroimaging. 2019; 289:13–7.
26. Atmaca M, Korucu T, Caglar Kilic M, Kazgan A, Yildirim H. Pineal gland volumes are changed in patients with obsessive-compulsive personality disorder. J Clin Neurosci. 2019; 70:221–5.
27. Song J. Pineal gland dysfunction in Alzheimer's disease: relationship with the immune-pineal axis, sleep disturbance, and neurogenesis. Mol Neurodegener. 2019; 14(1):28.
28. van Dalum J, Melum VJ, Wood SH, Hazlerigg DG. Maternal Photoperiodic Programming: Melatonin and Seasonal Synchronization Before Birth. Front Endocrinol (Lausanne). 2020; 10(January):1–7.
29. Schwartz WJ, Klerman EB. Circadian Neurobiology and the Physiologic Regulation of Sleep and Wakefulness. Neurol Clin. 2019; 37(3):475–86.
30. Gunata M, Parlakpinar H, Acet HA. Melatonin: A review of its potential functions and effects on neurological diseases. Rev Neurol (Paris). 2019; 1–18.
31. Coon SL, Fu C, Hartley SW, Holtzclaw L, Mays JC, Kelly MC, et al. Single Cell Sequencing of the Pineal Gland: The Next Chapter. Front Endocrinol (Lausanne). 2019; 10:1–11.
32. Farias Altamirano LE, Freites CL, Vásquez E, Muñoz EM. Signaling within the pineal gland: A parallelism with the central nervous system. Semin Cell Dev Biol. 2019; 95:151–9.
33. Barbosa Lima LE, Muxel SM, Kinker GS, Carvalho-Sousa CE, Silveira Cruz-Machado S, Markus RP, et al. STAT1-NFκB crosstalk triggered by interferon gamma regulates noradrenaline-induced pineal hormonal production. J Pineal Res. 2019; 67(3):1–12.
34. Maruani A, Dumas G, Beggiato A, Traut N, Peyre H, Cohen-Freoua A, et al. Morning Plasma Melatonin Differences in Autism: Beyond the Impact of Pineal Gland Volume. Front Psychiatry. 2019; 10(11):1–9.
35. Oliveira PF, Sousa M, Monteiro MP, Silva B, Alves MG. Pineal Gland and Regulatory Function. Second Edition. Vol. 1, Encyclopedia of Reproduction. Elsevier; 2018. 472–477.
36. Park J, Han JW, Suh SW, Byun S, Han JH, Bae J Bin, et al. Pineal gland volume is associated with prevalent and incident isolated rapid eye movement sleep behavior disorder. Aging (Albany NY). 2020; 12(1):884–93.
37. Grosshans M, Vollmert C, Vollstaedt-Klein S, Nolte I, Schwarz E, Wagner X, et al. The association of pineal gland volume and body mass in obese and normal weight individuals: A pilot study. Psychiatr Danub. 2016; 28(3):220–4.
38. Peres MFP, Valença MM, Amaral FG, Cipolla-Neto J. Current understanding of pineal gland structure and function in headache. Cephalalgia. 2019; 39(13):1700–9.
39. Han Q, Li Y, Wang J, Zhao X. Sex Difference in the Morphology of Pineal Gland in Adults Based on Brain Magnetic Resonance Imaging. J Craniofac Surg. 2018; 29(5):e509–13.
40. Karolczak K, Watala C. The Mystery behind the Pineal Gland: Melatonin Affects the Metabolism of Cholesterol. Oxid Med Cell Longev. 2019; 2019:4531865.
41. Hussain S. A. Effect of melatonin on cholesterol absorption in rats. Journal of Pineal Research. 2007; 42(3):267–271.
42. Lozada-Martínez I, Maiguel-Lapeira J, Torres-Llinás D, Moscote-Salazar L, Rahman MM, Pacheco-Hernández A. Letter: Need and Impact of the Development of Robotic Neurosurgery in Latin America. Neurosurgery. 2021; 88(6):E580-E581.
43. Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, Navarro-Coronado A, Moscote-Salazar L, Pacheco-Hernández A, et al. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. J Clin Neurosci. 2021; 88:219-225.
44. Ortega-Sierra MG, Durán-Daza RM, Carrera-Patiño SA, Rojas-Nuñez AX, Charry-Caicedo JI, Lozada-Martínez ID. Neuroeducation and neurorehabilitation in the neurosurgical patient: programs to be developed in Latin America and the Caribbean. J Neurosurg Sci. 2021 Jun 10.
45. Ortega-Sierra MG, Prado-Grajales V, Martinez-Imbett R, Unás-Perea K, Lozada Martinez ID. Research career in

neurosurgery: a challenge for future neurosurgeons. J Neurosurg Sci. 2021 Aug 3.
46. Blanco-Teherán C, Quintana-Pájaro L, Narvaez-Rojas A, Martínez-Pérez R, García-Ballestas E, Moscote Salazar L, et al. Evidence-based medicine in neurosurgery: why and how? J Neurosurg Sci. 2021 Aug 3.
47. Lozada-Martínez ID, Díaz-Castillo OJ, Pearson-Arrieta AC, Galeano-Buelvas A, Moscote-Salazar LR. Post-COVID 19 neurological syndrome: A new risk factor that modifies the prognosis of patients with dementia. Alzheimers Dement. 2021 Sep 5.