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CHRONIC FATIGUE SYNDROME IS AN OBSCURE INFLAMMATORY DISEASE LACKING THERAPY WHICH ALSO AFFECTS COVID-19

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ABSTRACT

Chronic fatigue syndrome (CFS) is characterized by physical and mental tiredness with muscle fatigue, headache, and joint pain. This disease can additionally present mental disorders such as depression, mood swings, and "brain fog". CFS affects women more than men with an incidence 4 times higher in women, and the diagnosis is often difficult to assess. The cause of CFS is still unknown, and the disease can last for years and can cause neurological disorders. Patients affected by this dysmetabolic syndrome do not improve with rest and the therapy does not make use of specific markers because they do not exist. CFS is often correlated with humoral immune dysfunction. Patients with SARS-CoV-2-induced COVID-19 were recently observed to present with CFS. The inflammatory disease is mediated by the pro-inflammatory cytokines IL-1, TNF, and IL-6 which are released by microglial cells activated by the SARS-CoV-2 virus. Laboratory tests that aid in the diagnosis of CFS are blood cytometry and urinalysis, measurements of thyroid hormones T3 and T4, C-reactive protein, and blood phosphorus levels, and metabolic panel analysis. More in-depth future studies may lead to a better diagnosis and therapy that takes into account specific biomarkers.

KEYWORDS: *chronic fatigue syndrome, immunity, COVID-19, SARS-CoV-2, inflammation, CNS*

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by severe tiredness that can worsen with physical and/or mental activity (1). In addition to chronic fatigue, patients affected by this disorder may also present headache, light sensitivity, muscle and joint pain, difficulty concentrating, depression, and mood swings (2,3) (Table I). Additionally, CFS can produce sleep disturbances, mental cloudiness, and worsening of symptoms with physical activity (4). Patients with CFS experience persistent tiredness that can be combined with other disorders, and the diagnosis is often difficult since symptoms are often underestimated or poorly understood. The disease affects more women than men (with women affected about 4 times more often than men) and usually occurs between the ages of 20 and 40, even though it can also occur in children and adolescents (5). Fatigue can be acute or chronic, can be triggered by stress, and can manifest itself in various forms (6). Sometimes symptoms can be alleviated or resolved with rest and by improving the diet or doing physical exercises (7). A healthier lifestyle can help to alleviate the symptoms of CFS. Chronic diseases, such as

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rheumatoid arthritis, multiple sclerosis, stroke, systemic lupus erythematosus, some psychiatric disorders, and tumors, can induce chronic fatigue (8).

Table I. *Symptoms that may accompany chronic fatigue syndrome (CFS).*

- Severe fatigue
- Polyarthralgia
- Sleep disturbances
- Sore throat
- Muscle weakness and pain
- Joint pain
- Headache
- Irregular heartbeat
- Difficulty concentrating
- Chills and night sweats
- Tender lymph nodes in the neck or armpits
- Depression
- Digestive issues, like irritable bowel syndrome
- Allergies and sensitivities to foods, odors, chemicals, light, or noise
- Shortness of breath

DISCUSSION

In subjects suffering from CFS, tiredness remains even after resting, and it can appear suddenly and can last for years (9). The disease has an unknown cause and can affect individuals of any age, although it usually appears at middle-age. CFS initially appears like a cold, with typical cold-like symptoms, that can be different from person to person (10). Afterwards, patients go on to experience tiredness, effort fatigue, cognitive problems, and other dysfunctions such as disorders in which the sympathetic, parasympathetic, and enteric systems of the autonomic nervous system are affected. CFS is not relieved by rest and may be accompanied by other pathological symptoms including dysfunction of cellular metabolism, and abnormalities with the endocrine system and ion transport (8).

Fukuda et al. described some clinical diagnostic criteria for this neurological disorder, where it was highlighted that for the disease to be such it had to have at least a 50% reduction in physical activity (11). This neurological diagnostic procedure was approved by the scientific community since there are no specific biomarkers or particular methods to reveal the disease (9).

The pathogenesis of CFS appears to be related to the humoral immune system (12). It has been noted that CFS can be triggered by infectious diseases, including viral ones, exposure to toxic substances, and stressful living conditions (13). The diagnosis should always consider both the severity and duration of the disease. Individuals suffering from CFS should undergo laboratory tests such as blood cytometry, urine analysis, T3 and T4 thyroid hormone tests, measurement of C-reactive protein and phosphorus blood levels, and metabolic panel analysis (14). However, laboratory tests by themselves are not satisfactory, even if they serve to exclude other pathologies, since the symptoms of CFS may look like other medical conditions (15). Affected patients should closely monitor their health to help perform a more accurate diagnosis.

To date, there is no cure for CFS, although some treatments can help to alleviate the symptoms in some cases. Treatments must consider the patient's overall health, medical history, and drug tolerance. To date, there is no specific therapy for this disease and therefore, non-specific treatments are utilized, which can include the use of non-steroidal anti-inflammatory drugs, antidepressants, physical exercise, psychotherapy, and in some cases, cortisone (16). Additionally, vitamin supplements and antioxidants can alleviate the symptoms in some cases (17). The rate of clinical depression in CFS patients is between 36% to 70% and affected subjects should undergo an examination of their general mental state (18). To date, drug therapy is limited, but cognitive therapy and exercise therapy often improve fatigue, anxiety, and quality of life (19).

CFS is a very complex disease and may involve dysfunction of the immune system. Some studies report that patients may have decreased antibodies with abnormal changes in B cells, T cells, and cytokines and chemokines (20). The symptoms of CFS often overlap with those of viral infections and the etiology of the disease is unclear (21).

CFS is a disease involving the CNS that is similar to fibromyalgia (22). The difference between these two nervous system disorders is that in fibromyalgia, the diagnosis is made by recognizing the inflammatory trigger points, while in CFS, there can be a low degree of systemic inflammation mediated by inflammatory cytokines induced by a specific agent such as a virus, including SARS-CoV-2.

Chronic fatigue syndrome and COVID-19

Certain viral infections can trigger CFS post-infection, including infection by SARS-CoV-2 that induces COVID-19 (23). COVID-19 first appeared in China and caused an international pandemic emergency with over five million deaths globally. This disease can provoke severe acute respiratory syndrome and flu-like symptoms. It has been reported in biomedical literature that after a few weeks or months of infection with the SARS-CoV-2 virus, some patients presented fatigue and other symptoms, called long COVID (23). Long COVID is a multisystem pathology that can be very serious, is associated with the age of the patient, and mainly affects non-hospitalized subjects.

After an acute phase, COVID-19 can cause fatigue and physical tiredness that persist even with rest, characteristic symptoms of CFS (24). Patients with this disorder can suffer from severe mental fatigue called “brain fog”, muscle pain and weakness, migraines, palpitations, anxiety, dyspnea, and sleep disturbances (25). These symptoms appear after COVID-19 and in extreme cases, can even last for a few years.

Other post-infectious virus phenomena such as Borrelia Burgdorferi, Epstein-Barr virus, and cytomegalovirus can also cause CFS (26). These infections are increased in patients previously infected with SARS-CoV-2. CFS occurs with much less incidence in vaccinated patients. Vaccination, cognitive therapy, and exercise therapy often improve fatigue, anxiety, and quality of life.

Bacterial infections can also trigger CFS, although the biochemical and molecular mechanisms are still being studied (27). The clinical and neuropsychiatric diagnosis of the disease, which includes cognitive aspects, often relies on the help of a neurologist and a psychologist. CFS is often associated with depression and anxiety, serious symptoms that can even lead to suicide (7). The acute phase of COVID is accompanied by manifestations of muscle weakness and tiredness and can cause damage to organs such as the lungs and heart (23). In CFS, the ability to generate energy is lost and breathing capacity can also be reduced (28).

CFS patients have less energy than healthy people and should exercise more to improve their condition. However, exercise increases levels of IL-1, a pro-inflammatory cytokine that mediates the increase in corporeal temperature (10). In addition, CFS is mediated by high levels of lactate with defective metabolism (increased acidosis in the peripheral circulation, and muscles) (29). In severe cases of the disease, a defect in glycolysis may also occur (30). In CFS, patients show cognitive impairment with verbal difficulty and slowed cognitive functioning. These effects are due to low grade brain inflammation caused by pro-inflammatory cytokines such as IL-1, TNF, and IL-6 that are produced by microglial cells after activation with SARS-CoV-2 through the TLR receptor (24). These effects may decrease with physical exercise as the patient's physiological condition improves. Therefore, CFS must be diagnosed accurately and quickly to avoid serious complications.

CONCLUSIONS

At the moment, there are no specific treatments for CFS. Non-specific pharmacological treatments can reduce inflammation and pain and can be useful. Furthermore, exercise can help improve memory and cognitive functioning, and the use of light and noise protection devices, and the consumption of healthy and easily digestible foods, may help alleviate symptoms. However, drug therapy is limited and vaccination against COVID-19, cognitive therapy, and exercise therapy can improve fatigue, anxiety, and quality of life for the patient.

Conflict of interest

The author declares that they have no conflict of interest.

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PHEOCROMOCYTOMA IS A RARE TUMOR WITH A DIFFICULT DIAGNOSIS THAT USUALLY CAUSES HYPERTENSION

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ABSTRACT

Pheochromocytoma is a rare neuroendocrine tumor, with a prevalence rate of less than 0.1%, that is difficult to diagnose and treat. The tumor originates from the chromaffin cells of the adrenal gland and affects women more than men. The diagnosis is often confused with other disorders such as preeclampsia, eclampsia, and thrombocytopenia. The disease causes secondary hypertension that can be followed by stroke, myocardial infarction, and death, and mechanical effects such as palpation of the abdomen at the adrenal glands can cause paroxysmal seizures. In patients suffering from this disease, the skin may appear light brown and this sign can help with diagnosis. Headache, sweating, and especially hypertension are important diagnostic indicators for pheochromocytoma. Hyperglycemia, hypercalcemia, proteinuria, and the presence of lactic acid in the blood can also be diagnostic aids. Routine clinical tests may include catecholamine and urine measurements, and other diagnostic tests utilizing magnetic resonance imaging (MRI) and computerized tomography (CT), and scintigraphy allow the localization of the tumor.

KEYWORDS: *pheochromocytoma, diagnosis, neuroendocrine, tumor, hypertension*

INTRODUCTION

Neuroendocrine tumors are very rare and can be benign or malignant with different pathogenicity (1). Their heterogeneity causes difficulty with diagnosis and therapy (2). Pheochromocytoma is a rare tumor that arises from the chromaffin cells of the adrenal gland that secrete catecholamines (3). It is present in less than 0.1% of hypertensive patients (4). Pheochromocytoma can occur at any age but is more common after the age of 30. The tumor affects women more than men, but not in childhood, where it seems to prevail slightly in the male sex, and it is more frequent between the ages of 8 and 14 (5). In pheochromocytoma patients, severe hypertension is often present, but not all patients have paroxysmal episodes (6). During pregnancy, the disease occurs in 1 case in 50,000 and often leads to maternal-fetal mortality (7). Pheochromocytoma is difficult to diagnose and can be confused with other pathologies such as preeclampsia, eclampsia, and thrombocytopenia (8).

DISCUSSION

Pheochromocytoma can produce secondary hypertension, stroke, myocardial infarction, and death (9). The diagnosis is based on the symptomatic results represented by paroxysmal attacks with headache, sweating, palpitations, anxiety,

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and chest or abdominal pain. Additionally, patients may also experience nausea, vomiting, tremor and weakness, weight loss, and reduced breathing (10).

Pheochromocytoma patients present hypertension with a frequency of over 90% and can have an episodic form of the disease with paroxysmal or stable crises (11). The evidence of orthostatic hypotension, followed by clinostat hypertension, should be highlighted (12). Palpation of the patient's abdomen in correspondence with the adrenal glands can cause paroxysmal crisis, suggesting the hypothesis of pheochromocytoma (12). There may be light brown skin patches that suggest neurofibromatosis (13). In pheochromocytoma, tachycardia can also occur quite frequently, and there can also be reflex bradycardia during a hypertensive crisis, as well as a normal or even reduced heart rate (14).

In pheochromocytoma, there is often hyperglycemia linked to carbohydrate intolerance, accompanied by hypercalcemia and the presence of lactic acid in the peripheral blood (15). If the patient has severe hypertension, proteinuria may also occur (16). Many diagnostic tests, such as the measurement of plasma catecholamines or 24-hour urine, can only be performed in hospital or on an outpatient basis (17). Therefore, unfortunately, the diagnosis may not be immediately available.

Another diagnostic index is represented by the dosage of norepinephrine and epinephrine in the urine over 24 hours (18). After having ascertained the hypersecretion of catecholamines, procedures can be performed to search for the location of the tumor through magnetic resonance imaging (MRI) and computerized tomography (CT) of the abdomen (19,20). Scintigraphy can be useful in some cases, but not ultrasound (21).

However, the triad represented by headache and sweating that is accompanied by hypertension is a diagnostic index for pheochromocytoma (22). Other symptoms include panic attacks, hyperthyroidism, thyrotoxicosis, ischemic heart disease, amphetamine intoxication, menopause, and migraines (23). The presence of these diagnostic signs, especially combined with hypertension, is evidence to support the diagnosis of pheochromocytoma (24) (Table I). Hypertension is the most important diagnostic sign as it is almost always present. The patient with severe hypertension must be treated pharmacologically and the blood pressure must not be lowered quickly, bringing the diastolic pressure below 120 mm/Hg (25).

Table I. *Some of the clinical exams and patient symptoms which are utilized for the diagnosis of pheochromocytoma.*

Clinical exams:	Complete blood count, screening for electrolytes, urea nitrogen, creatinine, blood reticular acid measurements.
History of symptoms:	Anxiety, headache, sweating, heart palpitations, abdominal pain, chest pain, and weight loss.

Today, diagnostic imaging has significantly improved, and the localization of lesions is more precise, with better specificity and sensitivity. In addition, nuclear medicine provides a more powerful imaging modality than planar imaging, providing important information about the location and quality of lesions (26).

CONCLUSIONS

Pheochromocytoma is a tumor that forms in the adrenal medulla and is hormonally active. The tumor most often presents with hypertension, which is the most important diagnostic parameter. Patients suffering from this disorder may present paroxysmal attacks with headache, sweating, palpitations, anxiety, chest pain, and more rarely, nausea, vomiting, tremor, weakness, weight loss, and reduced breathing. The diagnosis of pheochromocytoma is difficult and often confused with more common pathologies such as preeclampsia, eclampsia, and thrombocytopenia. However, clinical exams such as MRI, CT, and scintigraphy allow for localization of the tumor.

Conflict of interest

The authors declare that they have no conflict of interest.

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FUNCTION AND MECHANISM OF ACTION OF ALPHA-METHYLDOPA: AN UPDATE

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ABSTRACT

Methyldopa is a central α-2-adrenergic receptor agonist capable of reducing blood pressure by relaxing and dilating the vessels. α-methyldopa allows blood to flow faster and for its sufficent supply to the tissues. At the level of the sympathetic nervous system, the metabolization of α-methyldopa by neurons leads to the formation of methylated norepinephrine, which is less active than norepinephrine on nerve impulses. The nerve impulses allow the release of the "false neurotransmitter", α-methyl norepinephrine, which exerts a weaker response than the peripheral effector, an effect which is also exerted on the blood vessels. Direct stimulation with α-methyldopa produces an active, or in some cases, slightly reduced response of the post-ganglionic sympathetic system, and so methyldopa does not block the response to direct stimulation of the postganglionic sympathetic system in the vessels. In experimental animals, methyldopa has been seen to suppress vascular resistance and reduce blood pressure without affecting post-ganglionic sympathetic activity. In some neurodegenerative diseases, such as Parkinson's disease (PD), there is a reduction in dopamine which leads to reduced mitochondrial respiratory activity and lower alpha-ketoglutarate dehydrogenase activity.

KEYWORDS: *alpha-methyldopa, neurotransmitter, L-Dopa, CNS, Parkinson's disease, neurodegeneration*

INTRODUCTION

α-methyldopa, a methylated analogue of L-Dopa, is part of the biosynthetic pathway that leads to the synthesis of norepinephrine under physiological conditions (1). Part of the α-methyldopa is converted into α-methyl dopamine by the action of the Dopa-decarboxylase enzyme, which in turn is transformed into α-methyl norepinephrine by the β-hydroxylating enzyme (2). The antihypertensive effect of α-methyldopa is characterized by a marked decrease in peripheral vascular resistance without significant changes in cardiac output (3). This effect is accompanied by a selective reduction in renal circulation resistance with a consequent increase in glomerular flow (4). The mechanism through which α-methyldopa determines these hemodynamic effects is not yet clear and is still the subject of numerous studies and experimental investigations. From a biochemical point of view, the pharmacological action of methyldopa is different than other antihypertensive drugs and simple to understand (5). In fact, the exact correlation between the observed pharmacological effects and the biochemical events induced by this simple analogue in metabolism leading to the biosynthesis of the adrenergic neurotransmitter is not yet completely established (6).

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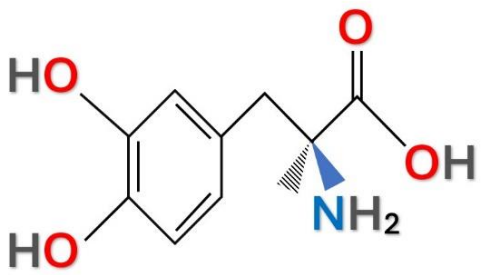

Fig. 1. *Chemical structure of α-methyldopa, a methylated analogue of L-Dopa.*

DISCUSSION

In the sympathetic neuron, the metabolic use of α-methyldopa, a natural precursor L-dopa, leads to the formation of methylated norepinephrine which proves to be substantially less active than norepinephrine regarding the transmission of nerve impulses at the sympathetic level (7). For this reason, α-methyl norepinephrine is referred to as a "false neurotransmitter" (8). One of the main mechanisms of action of methyldopa is the formation of α-methyl norepinephrine, which replaces the real neurotransmitter in the deposits located at the sympathetic nerve endings (9). Upon the arrival of nerve impulses, the release of the "false neurotransmitter" results in a much milder response of the peripheral effector, i.e., with a reduction in vascular tone and the vasoconstrictor response (10). In fact, the administration of α-methyldopa in experimental animals results in a depletion of tissue deposits of norepinephrine and the appearance of methyl norepinephrine. However, the formation of the "false transmitter" and the consequent reduction of peripheral sympathetic activity does not yet fully account for the pharmacological effects induced by α-methyldopa (11).

In animals treated with α-methyldopa, the response to direct stimulation of the post-ganglia sympathetic system does not appear blocked, but only partially reduced in some cases, and even normal in others (12). Thus, methyldopa, even in large doses, does not block the response to direct stimulation of the postganglionic sympathetic system in the heart and in peripheral vascular resistance (13). For example, in dogs, it has been demonstrated that methyldopa decreases the vascular resistance of the innervated limbs without causing an appreciable decrease in post-ganglionic sympathetic activity (1).

Numerous clinical studies have also confirmed that methyldopa reduces blood pressure in humans, both in an upright or supine position (3). In these cases, the simple inhibition of the peripheral sympathetic nervous system does not seem to be sufficient to explain the mechanism of action of methyldopa. It therefore seems logical to think that other factors intervene in determining the pharmacological response to the substance. Worthy of particular interest is the hypothesis that reduced adrenergic activity in the central nervous system (CNS) is also responsible, at least in part, for the effects of methyldopa (14).

Today, the formation of methyl norepinephrine from methyldopa in the adrenergic centers of the CNS is known. It is hypothesized that the hypotensive action of methyldopa is partly due to the formation of methyl norepinephrine in the brain, which replaces the much more potent natural neurotransmitter (15). Consequently, there is a notable decrease in sympathetic activity of central origin, which in turn is responsible for the fall in peripheral vascular resistance (16). The administration of a potent peripheral inhibitor of the Dopa-decarboxylase enzyme does not prevent the hypotensive action of methyldopa. In other words, when the formation of methyl norepinephrine ("false neurotransmitter") is blocked in the peripheral sympathetic, but not in the central adrenergic pathways, a drop in peripheral vascular resistance still occurs (17). A plausible explanation for this fact is that the formation of the "false neurotransmitter" in the CNS results in a substantial reduction in the activity of the adrenergic centers, which in turn are responsible for peripheral vascular responses (18).

This is supported by various clinical studies and experimental research. For example, in experimental animals, the infusion of methyldopa into the vertebral artery reduces systemic arterial pressure (19). The same dose injected intravenously into the peripheral circulation does not significantly change blood pressure values (20). The hypotensive effect of small doses of methyldopa injected into the vertebral artery is abolished by pre-treatment with an inhibitor of the Dopa-decarboxylase enzyme that can cross the blood-brain barrier (BBB) (19). However, if an inhibitor that does not cross the BBB is used, the action of methyldopa is not blocked. From these data it seems suggestive to conclude that an important part of the mechanism of action of the drug is carried out through a decrease in central adrenergic activity and

that this decrease occurs mostly due to the increase of methyldopa in the biosynthetic chain of norepinephrine, leading to the formation of a "false neurotransmitter" such as α-methyl norepinephrine (21).

Like other antidepressant drugs, α-methyldopa has been the subject of numerous studies from which an important observation emerged, which in a certain sense, characterizes and distinguishes this drug from the others. While it has been observed that treatment with reserpine, chlorothiazide, and hydralazine generally induces an increase in renin activity in the plasma, α-methyldopa substantially reduces renin levels both in laboratory animals and in hypertensive subjects (22). In dogs, intravenous administration of α-methyldopa for 7 and 10 days causes a decrease in plasma renin activity (from 13 μg/ml to 7 μg/ml) of the produced angiotensin II (23). Again, in dogs, α-methyldopa blocks the increase in renin produced by sympathetic stimulation of the kidney without preventing the vasoconstrictor effect induced by the stimulation itself (24). Also in this case, the effect of α-methyldopa does not seem to be attributable to a generic depression or blockade of adrenergic activity, but rather either to a specific effect of the drug at the sympathetic neurological level or to an effect on the CNS (25).

In this regard, it is interesting to observe that the "false neurotransmitter" α-methyl norepinephrine synthesized by the neuron from α-methyldopa is much less active than norepinephrine in stimulating renin secretion (26). In some experiments, it has been seen that the infusion of norepinephrine in dogs induces a clear increase in plasma renin, while the infusion of equivalent doses of α-methyl epinephrine is followed by a slighter increase in renin (27). The depressant action of α-methyldopa on the renin system does not seem to be mediated by modification of the electrolyte balance or by the secretion of aldosterone (28). These parameters are not modified in hypertensive subjects after administration of the drug. Even in the clinic, it has been confirmed that α-methyldopa substantially decreases renin activity both in normotensive subjects and in non-severely hypertensive patients with renal failure (29).

From all these observations, another important characteristic of α-methyldopa emerges which certainly deserves serious consideration in the analysis of the drug's mechanism of action. It is still unclear whether the suppression of renin activity is mediated exclusively by the action of α-methyldopa on the post-ganglionic sympathetic system, or whether it is also mediated by the action of the drug on the central adrenergic pathways (30).

α-Methyldopa and Parkinson's Disease

In 1817, James Parkinson first described Parkinson's disease (PD) as a disease characterized by a drastic decrease in dopamine. This neurodegenerative disease is the most widespread after Alzheimer's disease. PD is an extrapyramidal syndrome characterized by muscle rigidity that manifests with resistance to passive movements (31). Patients affected by this neurological disorder mainly present diffuse tremors and muscle hypertonicity. The tremors usually affect the muscles of the limbs and head. In the hands, the continuous movements of the thumb and forefinger resemble pilling or rolling movements. The patient has difficulty moving and tends to fixate on their facial expression, an effect called Parkinsonian mask (32). Tremor can also occur during a state of rest and can increase in cases of anxiety and bradykinesia, causing difficulty in starting and finishing movements. The course and symptoms of PD worsen over time, even though treatment with new drugs and non-pharmacological therapies have significantly improved patients' quality of life.

At an anatomopathological level, the disease presents progressive and prolonged neuronal degeneration of the "substantia nigra pars compacta" (33). In PD patients, the quantity of dopamine is significantly reduced, as is the concentration of neuromelanin with a consequent decrease in pigmentation (34). In addition, patients also present reduced mitochondrial respiratory activity and lower alpha-ketoglutarate dehydrogenase activity (35).

CONCLUSIONS

α-methyldopa is characterized by an antihypertensive effect and a marked decrease in peripheral vascular resistance without significant changes in cardiac output. Drastic decrease of dopamine characterizes PD which is a neurological disorder which presents muscle rigidity with resistance to passive movements. The therapies available today for PD involve dopamine replacement and other pharmacological treatments and help to prolong lifespan but are not sufficient to block the development of this disorder. Because the causes of the disease are not yet known, future studies should focus on this topic to develop therapies and improve prevention (34). In addition, the future goal of research should be to distinguish growth factors that can replace degenerated gray matter.

Conflict of interest

The author declares that they have no conflict of interest.

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THE CONCENTRATION OF SEROTONIN IN THE BRAIN IS DETERMINANT FOR ITS BIOLOGICAL RESPONSE

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ABSTRACT

Serotonin (5-HT) is a neurotransmitter that acts both in the central nervous system (CNS) and peripherally, and affects cell proliferation and migration. 5-HT plays a role in psychiatric diseases where it is deficient. 5-HT acts on smooth muscles where it can cause contraction or dilation and can also act on sensory nerve endings, causing pressor or depressor reflexes. 5-HT can cause contrasting biological effects. For example, 5-HT causes strong vasoconstriction in blood vessels, while in skeletal muscle vessels, it causes vasodilation. In the CNS, 5-HT participates in numerous functions such as the regulation of mood and sleep, the modulation of body temperature, sexuality, cognitive functions, and appetite. There are 4 classes of 5-HT receptors: slow-acting 5-HT2R which releases calcium ions (Ca^{++}), 5-HT4R, 5, 6, and 7, which increase cAMP, 5-HT1/5R which decreases cAMP, and fast-acting 5-HT3R that promotes the flow of Na^{+} or K^{++}. The 5-HT1AR receptor binds the 5-HT and is involved in the regulation of stress and tissue defence, while the 5-HT2AR receptor is a mediator of stress in the active phase. A more in-depth study on 5-HT and its reuptake, could lead to the discovery of new drugs for treating depression and neuropsychiatric diseases. Pharmacological treatment of neurological disorders due to changes in 5-HT levels can certainly improve the patient's quality of life.

KEYWORDS: *serotonin, 5-HT, neurotransmitter, psychiatric disease, CNS, 5-HT receptor*

INTRODUCTION

Serotonin is a biogenic amine that is produced by both the plant and animal kingdoms, including humans (1). In 1930, the Italian researcher Erspamer reported that tissue extracts from the gastrointestinal system contained particular cells called enterochromaffin, which caused the contraction of smooth muscles (2). The substance responsible for these biological effects was first called enteramine (3). Subsequently, Rapport, Green, and Page isolated a vasoconstrictor molecule similar to enteramine which they gave the name ‘serotonin’ or 5-hydroxytryptamine (5-HT) (4).

The biosynthesis of endogenous 5-HT derives from tryptophan, an essential amino acid that is introduced into the body through the diet and excreted in the urine. Tryptophan is converted into 5-hydroxytryptophan thanks to the action of tryptophan hydroxylase. Only 1% of introduced tryptophan is converted to 5-HT through a hydroxylase enzyme that adds a hydroxyl group to tryptophan at position 5 to form 5-hydroxytryptophan (5). Subsequently, the decarboxylase enzyme removes the carboxyl group to form 5-HT (6). The synthesis of 5-HT varies by species and tissue type, and in humans, 5-HT is mostly concentrated in platelets and brain and intestinal mucosa (7). Human immune cells, such as mast cells (MCs), do not contain 5-HT, while those of rodents, such as rats and mice, do contain it and it is stored in granules (8).

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5-HT is ubiquitous in the organism and is a neurotransmitter peptide along with other hormones such as substance P, somatostatin, and vasoactive intestinal polypeptide. Platelets in human blood contain the majority of 5-HT, which is degraded by the tissue enzyme monoamine oxidase (MAO) by removing the amino group and converting 5-HT into 5HIAA excreted in the urine (9). 5-HT mediates intestinal tissue contraction and peristalsis, coagulation, vasoconstriction, and many neurological functions (10). Macrophages treated *in vitro* with 5-HT are stimulated to phagocytosis, an important effect in the inflammatory process that could also be extended to brain microglial cells.

DISCUSSION

5-HT is a neurotransmitter implicated in psychiatric diseases. Most studies on this topic indicate that there is decreased availability of the 5-HT transporter in patients with psychiatric disorders (11). These studies suggest new avenues for anti-depressant treatment to elucidate response mechanisms to selective 5-HT reuptake inhibitors (SSRIs) and provide a basis for pharmacological treatment (12).

5-HT is stored in neurons, platelets, enterochromaffin cells, and MCs of rodents. The cytoplasmic granules of platelets contain 5-HT, whereas in neurons, 5-HT is synthesized locally in the synaptic vesicles of serotonergic nerves (13). When injected experimentally into the bloodstream, 5-HT does not reach the CNS because it is blocked by the blood-brain barrier (BBB) (14). However, when the BBB is disrupted, the brain, and other organs of the body, absorb 5-HT from the bloodstream and body fluids, while platelets, which do not synthesize 5-HT, only take it from the blood. The effectiveness of the biological contractive effect of 5-HT is verified *ex-vivo* through the contraction of strips of stomach or heart tissue of experimental animals (15). However, this effect depends on 5-HT concentrations.

The biological effects of 5-HT are variable and differ between animal species, between human individuals, and in different tissues. For example, 5-HT can cause vasoconstriction or vessel dilation on the smooth muscle of the cardiac vessels depending on the type of vessel on which it acts (16). At a cerebral level, 5-HT acts on nerve sensory endings where it can cause pressor or depressor reflexes (17). 5-HT causes strong vasoconstriction on denervated blood vessels (an effect which is not dependent on the CNS), while on skeletal muscle vessels, including cardiac ones, it causes vasodilation (18).

The intravenous effects of 5-HT on blood pressure initially show a short phase of vasodepression, and subsequently, a phase with increased pressure, and finally, there is a depressive phase with vasodilation. An increase in 5-HT can cause flushes on the skin due to venous constriction and blood deposited in dilated capillaries, while the lack of 5-HT can be the cause of headaches (19). 5-HT injected subcutaneously causes pain, erythema, and cyanosis, effects which are not caused by histamine, and which can be inhibited with a 5-HT antagonist (20). 5-HT mediates anaphylactic reactions, renal necrosis through vasoconstriction, and in some animals, shock caused by bacterial endotoxins (21). In rodents, 5-HT causes placental degeneration and abortion, and tissue destruction when injected into a tumor site (22). In addition, it can also cause tachycardia, palpitation, epigastric discomfort, and diarrhea.

5-HT plays a protective role for the human body against radiation and has a positive effect on wound healing. In fact, experiments on tissue lesions in rats have shown that 5-HT deficiency delays skin healing (23). Histamine, bradykinin, and angiotensin also belong to the 5-HT family. These substances, like 5-HT, have broad-spectrum biological activities with different functions at both a physiological and pathological level.

In the mouse, 5-HT binds to various receptors consisting of 7 gene families, with approximately 14 distinct subtypes participating in various transduction pathways (24). The 5-HT receptor 5-HT1AR is implicated in moderating stress and defending the brain against insults, while the 5-HT2AR receptor mediates active stress. In fact, antidepressants could improve the biological activity of 5-HT1AR by blocking the reuptake of 5-HT, while 5-HT2AR is increased by agonist substances (25).

5-HT that is released by the brain activates neurons through a complex process, which is dependent on an increase in 5-HT receptors. Most research regarding the involvement of 5-HT in psychiatric diseases suggests there is decreased availability of the 5-HT transporter in patients. 5-HT concentrations are important because at different concentrations neurons can respond differently, even in opposite ways. For example, at low to moderate concentrations, 5-HT can inhibit pyramidal neurons, while at higher concentrations, 5-HT enhances the effects on the firing of pyramidal neurons (26). Therefore, 5HT requires high concentrations to perform its biological effect on 5-HT1AR, while on 5-HT2AR, it requires lower concentrations. In the brain, 5-HT receptors are divided into four classes: a) slow-acting 5-HT2R which releases calcium ions (Ca^{++}), b) 5-HT4R, 5, 6, and 7, which increase cAMP, c) 5-HT1/5R which decreases cAMP, and d) fast-acting 5-HT3R that promote the flow of Na^{+} or K^{++}. Thus, at low or moderate concentrations, 5-HT reduces the pyramidal activity of neurons, while at higher concentrations, there may be a recruitment of fast-acting, disinhibitory 5-HT3Rs that are expressed on γ-Aminobutyric acid (GABA)ergic neurons in the cerebral cortex.

CONCLUSIONS

5-HT is an important neurotransmitter that can act on both migration and cell proliferation. This neurotransmitter is ubiquitous in the human body and is stored by neurons, platelets, and enterochromaffin cells. 5-HT can cause both the contraction and release of smooth muscles, depending on the type of target tissue and its concentration. 5-HT, which is degraded by MAO, by binding its receptors 5-HT1AR or 5-HT2AR, can be a mediator of stress and psychiatric disorders. Depression can be treated pharmacologically with serotonergic drugs that improve the patient's cognitive phase and quality of life. However, future studies are necessary to illuminate more precisely the true biological role of 5-HT.

Conflict of interest

The author declares that they have no conflict of interest.

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NERVE GROWTH FACTOR DERIVED FROM SNAKE VENOM AND MOUSE SUBMAXILLARY GLANDS ARE SIMILAR AND SHARE SOME IMMUNOLOGICAL PROPERTIES

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ABSTRACT

Nerve growth factor (NGF) is an important molecule in neurobiology, which studies the structure, function, and activity of the nervous system in animal species. Subcutaneous injections of NGF in rodents cause an increase in the sympathetic ganglia of the para- and prevertebral chains until it reaches a volume 10-12 times that of the untreated ganglia. NGF communicates with the immune system by increasing the maturation, survival, and number of immune cells, particularly of mastocytes. In lymphocytes cultured *in vitro*, NGF exerts a proliferation action by binding to its TrkA receptor, induces the expression of T cell growth factor (IL-2), and modifies the shape of platelets. The antiserum from the mouse submaxillary gland counteracts NGF and exerts an inhibition identical to that caused by snake venom-derived NGF. The amino acid compositions of NGF derived from snake venom and mouse submaxillary glands are remarkably similar and sulfhydryl groups are absent in both. Here, we report that these two NGFs deriving from two different sources are the same molecule.

KEYWORDS: *nerve growth factor, NGF, venom, submaxillary gland, immunity*

INTRODUCTION

Nerve growth factor (NGF) is a neurotrophic peptide capable of influencing the development and growth of the nervous system (1). NGF can induce neurite growth in explants from sympathetic and sensory ganglia (2). This molecule is important for the role it plays in connecting the nervous system with the immune and endocrine systems. At the immune level, NGF provokes the maturation and survival of mast cells (MCs), the chemoattraction of basophilic granulocytes, and the proliferation of lymphocytes, induces the expression of the IL-2 receptor, causes the differentiation, survival, and chemotaxis of immune cells, and changes the shape of the platelets (3). There are various immune cells that interact with NGF and among these are lymphocytes and MCs. In both immune and endocrine cells, NGF uses the tropomyosin kinase (TrkA) receptor to transduce signals. Previous research has indicated the striking similarities between NGF derived from snake venom and NGF synthesized from mouse submaxillary glands (4,5).

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DISCUSSION

The NGF which is derived from snake venom and the NGF synthesized from mouse submaxillary glands share several biological properties. Both forms of NGF act specifically on sympathetic cells and embryonic sensory cells, producing an identical *in vivo* response that involves increases in both the number and size of nerve cells (6). Their specific activity *in vitro* is of the same magnitude, 10-8 to 10-9 g protein per biological unit.

Also from a chemical viewpoint, the NGF molecules have many characteristics in common. They are proteins with molecular weights all ranging from 25 Kd to 35 Kd. The amino acid compositions are remarkably similar and sulfhydryl groups are absent. Their biological activity is not lost when treated with organophosphorus compounds, although there is a progressive loss of biological and immunological activity with progressive oxidation of tryptophan residues.

Immunological data also favor a partial identity of some NGF preparations. Cross-reaction of mouse salivary gland NGF antiserum with crude Agkistrodon piscivorus venom NGF has already been shown by other authors, based on inactivation of the biological activity *in vitro* (7). Later, a degree of cross-reactivity for Crotalus adamanteus venom NGF was confirmed in micro-complement fixation experiments (8).

These immunological studies were extended by using NGF from mouse submaxillary glands and the venom of poisonous snakes. Specific monovalent antiserums were used in these preparations. NGF from mouse salivary glands and snake venom were prepared according to procedures designed in the laboratory. Mouse preparations met several homogeneity criteria. NGF from venom was a purified preparation obtained by isoelectric focusing of crude venom (9). Antiserums to mouse salivary gland NGF and to snake venom NGF were prepared in rabbits following an immunization.

Immunological activity was investigated by micro-complement fixation immunodiffusion, and by *in vitro* inhibition of NGF activity. The results were obtained from *in vitro* inhibition experiments. The antiserum to mouse salivary gland NGF inhibited the biological activity of the venom tested. The degree of cross-reactivity was between 10% and 20%. The antiserum to snake venom NGF, although showing a higher titer with its homologous antigen, inhibited the NGF activity from the other sources to a lesser extent. The percentage of cross-reactivity with other venom NGF was between 5 to 10%.

With mouse salivary gland NGF, the cross-inhibition was less than 1%. When tested on agar plate, the antiserum to venom NGF gave distinct bands with the NGF of the venoms studied. The reactions between homologous and heterologous antigens were identical. No precipitation reaction was obtained when the venom antiserum was confronted with NGF from the mouse salivary gland (did not precipitate the NGF that was used). However, with venom from different snakes, NGF at a higher concentration than the mouse salivary gland NGF, a precipitation band was obtained, which fused with that of the homologous antigen.

The immunological relationship between the snake venom NGF and mouse submaxillary gland NGF was further explored using micro-complement fixation. A sharp peak was obtained against its diluted antiserum, but no complement fixation was obtained even when the antiserum concentration was increased using mouse salivary gland NGF as an antigen. When the antigen to the mouse salivary gland NGF was used, 80% complement fixation was obtained against its homologous antigen. Under these conditions, venom NGF showed traces of complement-fixation activity. When the antiserum concentration was raised ten-fold, a clear-cut peak of complement fixation approaching that found with the homologous antigen was obtained.

The results reported above further support the concept that the NGFs from all animal sources belong to a family of closely related proteins whose mechanism of action on the responsive nerve cells must be essentially the same. The antibodies elicited by the salivary gland NGF are clearly able to cross-react with identical antigenic sites on the venom NGF molecule (10). The two molecules must, in fact, be very similar if one takes into consideration the identical reaction obtained by immunodiffusion and the similarity index obtained by fixation of the micro complement with NGF from venom and the antiserum for NGF from mouse salivary glands.

CONCLUSIONS

NGF is a neurotrophic peptide discovered approximately 60 years ago by Rita Levi-Montalcini et al. as a protein that induces the growth of nerves (11). NGF works by binding to its TrkA receptor and is considered a target for the treatment of neurodegenerative diseases. NGF can be synthesized from mouse submaxillary glands and from snake venom. In this article, it is shown that the two NGF molecules synthesized from two different sources, the snake venom and mouse submaxillary glands, have the same biochemical size and are therefore, the same protein. In addition, the NGFs derived from the two sources act similarly on embryonic cells, producing both an increase in the number and size of nerve cells. Therefore, it can be concluded that the two molecules are the same molecule that exerts the same biological effect on nerve cells.

Conflict of interest
The authors declare that they have no conflict of interest.

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DISRUPTION OF THE EXTRAPYRAMIDAL SYSTEM - WILSON'S DISEASE

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ABSTRACT

The extrapyramidal system (EPS) includes both nerve centers and bundles of nerve fibers that are controlled by the niger locus and the subthalamic nuclei. The EPS is involved in the control of body position and movements, and the contraction of skeletal muscles, contibuting to voluntary movement as well as playing a key role in automatic movements. When the EPS is disrupted, central nervous system (CNS) disorders with akinesia, tremor, athetosis, chorea, and hyperkinesia can occur, as is highlighted in Parkinson's disease (PD). In chorea, which can involve the face, mouth, trunk and limbs, involuntary and repetitive, short, irregular and rapid movements can occur. In addition, neurological syndromes and disorders of uremic pathology due to chronic kidney disease may also occur. Disruption of the EPS at a certain level can also cause stiffness and suppression of reflexes. In the injured EPS, there may be hypotonic muscles before contraction (and more rarely, hypertonia), with the presence of grimaces on the face, speech disorders, and dysarthria. Involuntary, abrupt, and arrhythmic choreic movements may occur suddenly and are often accompanied by muscle hypotonia, and there may be torsional spasms consisting of slow muscle contractions. In the genetic disorder Wilson's disease (WD), which is characterized by copper metabolic dysfunction, neuronal degeneration affecting axons may be present.

KEYWORDS: *extrapyramidal system, CNS, copper, neurodegeneration, axon, Wilson's disease*

INTRODUCTION

The extrapyramidal system (EPS) is a complex circuit of nerves that includes both nerve centers and the bundles of nerve fibers that connect the centers to the rest of the central nervous system (CNS) (1). The EPS is under the control of the locus niger and the subthalamic nuclei (2). The main parts of this system include the central grey nuclei, caudate nucleus, globus pallidus, putamen, and thalamus, including the area of the cerebral cortex of the frontal lobe (3). The EPS includes the structures of the CNS that contribute to the control of the position and movements of the body and the contraction of the skeletal muscles, contributing to the maintenance of body posture (4). The EPS is involved in voluntary movement and also plays a key role in automatic movements such as walking. Dysregulation in the EPS can lead to CNS disorders, including Wilson's disease (WD) which involves copper metabolic dysfunction.

DISCUSSION

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Damage to the EPS can cause CNS dysfunction characterized by akinesia, tremor, and hyperkinesia, clinical signs that occur especially in Parkinson's disease (PD) (5). Extrapyramidal hypertonia is very characteristic of PD and involves the upper limbs which are prevented from extending due to limb rigidity (6). Disruption of the EPS at the level of the striatum is characterized by muscular rigidity, consequent disturbances of postural tone and coordinated movements, and the appearance of involuntary movements such as tremors, athetosis, and chorea (7).

Chorea usually involves the face, mouth, trunk, and limbs and is characterized by repetitive, brief, irregular, and rapid and involuntary movements that begin in one part of the body and move abruptly, unpredictably, and often continuously, towards another side (8). Rigidity can manifest in various ways depending on the height of the interruption of the extrapyramidal pathways. If the interruption extends from the quadrigeminal tubercles to an area located at the level of the red nucleus, the rigidity is intense and accompanied by the suppression of reflexes. If the extrapyramidal pathway is interrupted below the striatum, there is rigidity of decerebration (9). However, if the damage occurs at the level of the skull, excluding the connections of the basal nuclei with the extra-pyramidal areas of the cortex, there is still rigidity, but the reflexes persist and this case is called decortication rigidity (10).

The alteration of the basal nuclei has consequences that depend on the severity of the damage. Athetotic movements can be unilateral or bilateral, are generally absent during sleep, and are accentuated immediately before voluntary movements (11). The muscles involved are generally hypotonic before contraction, but more rarely there is hypertonia. Affected subjects often have the appearance of grimaces on their faces. The muscles of the tongue can also be involved, as well as the palate, resulting in speech disorders and dysarthria (12). Choreic, involuntary, abrupt, and arrhythmic movements can appear suddenly and are often accompanied by muscular hypotonia (13). Patients may also present with torsion spasms consisting of slow muscle contractions that lead to severe twisting of the trunk and limbs (14). Other abnormal movements are called hemiballismus which are rapid and sudden, similar to choreic ones, while spasms consist of a long-lasting contraction of the muscle bundles with sometimes accompanied by pain (15). The main diseases associated with damage in the basal nuclei are: WD, PD, athetotic syndromes, choreic syndromes, and hemiballismus syndrome (16).

Wilson's disease (WD)

WD was described for the first time by Samuel Alexander Kinnier Wilson in 1912 (17). In an interesting article, he highlighted some fundamental characteristics of WD such as heredity, the concomitance of liver diseases (cirrhosis), and neurological deficits of the extrapyramidal type (18). The gene responsible for this rare disease is called ATP7B, which encodes a P-type ATPase that modifies the level of the $Cu2^{+}$ in the tissue and blood (19). In WD, copper metabolic dysfunction can cause isolated degeneration of neurons with axonal trafficking and peripheral sensory neuropathy (20) (Fig.1).

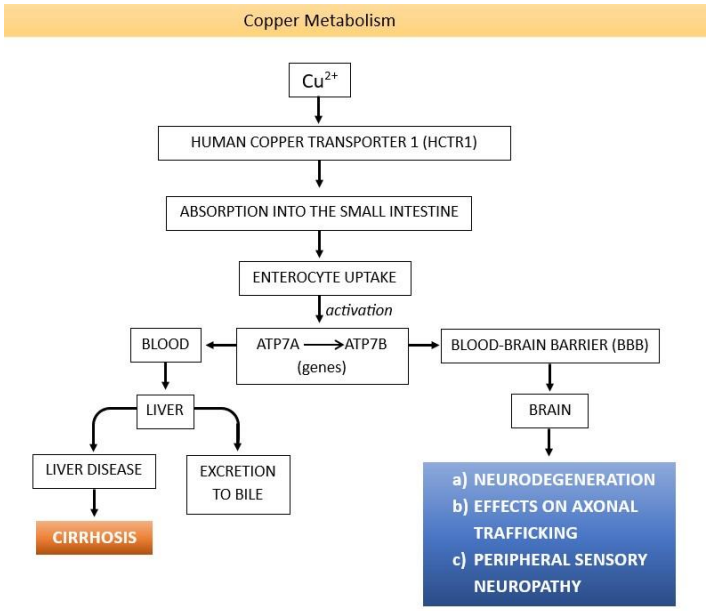

Fig. 1. *In Wilson's Disease (WD), copper metabolic dysfunction leads to liver disease such as cirrhosis and neurodegeneration, impaired axonal trafficking, and peripheral sensory neuropathy.*

The pathogenesis of WD is characterized by muscular rigidity, involuntary movements, emotional crises, and neurological symptoms, and non-neurological signs such as liver cirrhosis and greenish pigmentation of the cornea which can occur in some cases (20). The diagnosis is performed on clinical laboratory samples where low levels (below 200-350 mg/l) of serum ceruloplasmin can be found, but sometimes levels of this protein can also be normal (21). In addition, WD patients may present increased urinary copper excretion and increased hepatic copper content (22).

The muscle stiffness progressively affects the muscles at a systemic level, predominantly affecting the flexor muscles. The contracted muscles present a resistance that has been called "lead pipe". Active movements are difficult, as is the production of sounds or noises using the vocal organs (23). Swallowing may also be impaired. Involuntary movements manifest as diffuse tremors or athetotic movements with a continuous flow of slow, steady, and writhing movements. Patients may experience mood changes with a predisposition to crying and laughing (24). Muscle hypertonicity often leads patients to remain with their mouths wide open, but with essentially normal reflexes.

Neurological damage mainly occurs at the level of the base of the telencephalon, the putamen, in the caudate which works with the putamen to receive input from the cerebral cortex, and in the pallidum, the two internal portions of the lenticular nucleus of the striatum (25). Patients affected by WD are often distinguished into 3 types: hepatic, hepato-neurological, and predominantly neurological. Patients with neurological dysfunction present with hypokinetic and hyperkinetic extrapyramidal symptoms and often contract PD. Accumulation of copper in the brain leads to dysfunction of the basal ganglia with movement disorders (26). Hyperkinesia often results in attention deficit disorder (27).

WD causes increased concentrations of copper in the brain and liver which can be chelated by penicillin (28). Increased copper causes clinical disorders that are different from those caused by other heavy metals such as Alzheimer's and PD (20).

CONCLUSIONS

The EPS is controlled by the niger locus and the subthalamic nuclei and mediates both voluntary and involuntary movements and the contraction of skeletal muscles. Damage to the EPS is associated with CNS disorders, as occurs in PD. This class of pathologies is characterized by the level of disruption to the EPS which can involve various parts of the body and different muscles. WD is characterized by copper metabolism dysfunction and causes neuronal degeneration and axonal dysfunction. There is currently no satisfactory therapy for WD, and future research is indispensable to improve treatment and the quality of life for patients.

Conflict of interest

The author declares that they have no conflict of interest.

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