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Mild Neurocognitive Disorder: Clinical Manifestations and Treatment

Deterioro cognitivo leve: Manifestaciones clínicas y tratamiento

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Abstract:

The World Health Organization (WHO) estimates there are 50 million older adults with a cognition-related condition; this incidence is expected to increase in the coming years. Although Mild Cognitive Impairment (MCI) is not considered pathological, it is the intermediate stage between normal aging and the presence of some considerable cognitive alteration. Today, there are no treatments for mild cognitive impairment (MCI); nonetheless, there are therapeutic measures with positive results, among them Cognitive Stimulation (CS) and Transcranial Direct Current Stimulation (tDCS) which prevent the appearance of severe symptoms. This review aims to explore the therapeutic measures used in older adults with MCI.

Keywords:

Mild cognitive impairment, epidemiology, treatment

Resumen:

La Organización Mundial de la Salud (OMS) estima que existen 50 millones de personas de la tercera edad que tienen algún padecimiento relacionado con la cognición, se prevé que esta cifra aumente su incidencia en los próximos años. Si bien es cierto que el Deterioro Cognitivo Leve (DCL) no se considera patológico, si es la etapa intermedia entre el envejecimiento normal y la presencia de alguna alteración cognitiva mayor. Actualmente no existen tratamientos para el deterioro cognitivo leve (DCL), sin embargo, se cuenta con medidas terapéuticas con resultados positivos como la Estimulación Cognitiva (EC) y la Estimulación Transcraneal de Corriente Directa (tDCS) que ayudan en la prevención de la aparición de sintomatología grave. Esta revisión, tiene por objetivo explorar las medidas terapéuticas que se utilizan en las personas de la tercera edad que presenta DCL.

Palabras Clave*:*

Deterioro cognitivo leve, epidemiologia, tratamiento

INTRODUCTION

Estimates indicate that the number of people living with dementia will triple by 2040, going from 57.4 million to 152.8 million.[1] It is estimated that, in the United States, the annual cost of having a Neurocognitive Disorder is $590.78 US for mild dementia and US$25,510.66 for severe dementia.[2] In the case of Neurocognitive Disorders (NCD), it is relevant to highlight that, from the onset of mild symptoms such as Mild Cognitive Impairment (MCI), they are disabling since the first manifestations. Therefore, this work aims to examine pharmacological and non-pharmacological MCI preventive treatments. In the case of MCI, its study is imperative, since it is an intermediate phase between normal and pathological aging.[3] MCI manifests as a set of alterations in primary cognitive functions, i.e., in spatial orientation, language, visual recognition, and the reduction of mnemic function. This condition is also usually accompanied by behavioral changes.[3] MCI is considered a precursor to dementia and is usually located in an intermediate stage between normal aging and Alzheimer's type dementia. It is a reality that pharmacological treatments have not had the expected results, hence the importance of exploring new treatments that allow older people to enjoy health and, above all, a good quality of life.[4]

EPIDEMIOLOGY OF NEUROCOGNITIVE DISORDERS

World statistics

MCI is not a disease typical of older people since different diseases can cause cognitive deterioration; however, there is a much higher prevalence in people between 60 and 65 years of age.[5]

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In Latin America, the global prevalence is 11% of older people suffering from some form of dementia. Regarding sex, a significant difference is observed: in women, this prevalence is 6%, while in men it is 4%. Likewise, there are differences between the rural and urban populations. In the case of men in rural communities, it is 1%, while in urban places, it is 5%. On the other hand, it is still higher for women than men in rural and urban communities, where they represent 7% in urban communities and only 2% in rural communities.[6]

In a systematic review with meta-analysis carried out by Prince, Bryce, Albanese, Wimo, Ribeiro, and Ferri in 2013, it was found that the standard proportion of people over 60 years of age varied between 5% and 7% in most regions worldwide, with the highest rate in Latin America, 8.5% and considerably lower in the four subregions of sub-Saharan Africa 2%-4%. It is estimated that in 2010, approximately 35.6 million people had dementia worldwide, and this number is expected to double every 20 years, reaching 65.7 million in 2030 and 115.4 million in 2050. In 2010, 58% of all people with dementia lived in low- or middle-income countries, and this proportion is projected to increase to 63% in 2030 and 71% in 2050.[7]

National statistics.

In recent years, dementia has represented a primary public health concern due to its global presence and its significant impact in economic, social, and health terms. Despite this, Mexico has few reports based on formal evaluations that adopt a clinical approach that uses the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[8] The prevalence in Mexico is 7.3% and an incidence of 27.3 (1000 people/year) for Alzheimer's Disease (AD).[9]

At the national level, there are surveys that provide relevant data on the cognitive status of older people. The first is the Health Wellbeing and Aging Survey (SABE), which was applied from 2013 to 2015 at the national level in the following states of the Mexican Republic: Coahuila, Colima, Durango, State of Mexico, Guanajuato, Hidalgo, Michoacán, Morelos, Querétaro, San Luis Potosí, Tlaxcala, Yucatán, and Veracruz. Folstein's Mini-mental state examination instrument was applied in the cognitive state-related area, where the cut-off line to consider an older adult as suspected of cognitive impairment was a score equal to or less than 12 points.[10]

Table 1 shows the highest prevalence of cognitive impairment symptoms is in the State of Mexico at 22%, followed by Coahuila at 18.8%, Michoacán at 18.5%, Guanajuato at 16.2%, and at the end of the table, San Luis Potosí at 2.9%, Tlaxcala at 5.6%, and Durango at 6.2%.[10]

The National Survey on Health and Aging in Mexico (ENASEM) evaluates orientation through five specific questions. The data obtained from the survey revealed the following: in an age group of 58 years and older, 94.3% correctly answered what day of the week it was. Likewise, 90.6% correctly identified the month they are, the federal entity of residence, with 85.7 percent. The lowest percentages of correct answers were for the day of the month, with 67.9%, and the time of the interview, with 67.1%.[11]

Table 1. Cognitive *Impairment Prevalence in Mexico.*[10] *Results of the Health, Wellbeing and Aging Survey ≥60 age.*

State	Percentage of memory impairment	Men	Women
Estado de México	22%	41%	59%
Coahuila	18.8%	40.64	59.4%
Michoacán	18.5%	38.3%	61.7%
Guanajuato	16.2%	25.4%	74.6%
Querétaro	14.6%	38.3%	61.7%
Morelos	13.6%	39.8%	60.2%
Veracruz	12.8%	36.9%	63.1%
Yucatán	12.7%	34.3%	65.7%
Colima	9.5%	38.5%	61.5%
Hidalgo	6.7%	30.3%	69.7%
Durango	6.2%	34.6%	65.4%
Tlaxcala	5.6%	No data	No data
San Luis Potosí	2.9%	42.7%	57.3%

State statistics

In Hidalgo, two studies have been carried out in the municipalities of Actopan and Tlahuelilpan. The first found that approximately 16% of the population had a below-average score. It is important to note that, in this study, the Mini-Mental test was not used as usual but employed the Cognitive Abilities Screening Instrument (CASI).[12] The results of the second study showed a significant increase, with a percentage of 40.9% of people presenting probable cognitive impairment. To evaluate cognitive impairment Folstein's Mini-mental was used.[13]

MILD COGNITIVE IMPAIRMENT

The term Mild Cognitive Impairment (MCI), previously known as benign senile forgetfulness, age-related memory impairment or age-related cognitive decline, mild cognitive impairment (MCI) did not have a clinical description. In the 1980s, Reisberg et al.[14] placed this entity at level 3 of compatible functioning, describing it as follows:

"Objective functional impairment of sufficient severity to interfere with complex occupational or social tasks (ADL-C). For the first time, the patient forgets important appointments. From a psychomotor point of view, they can get lost in unknown places, although they do not have difficulties performing routine tasks (ADL-I)".[15]

In 1997, Petersen et al.[15] developed the first clinical criteria and listed them: (1) memory complaint, preferably corroborated by an informant. (2) objective memory decline for age and education. (3) predominantly normal general cognitive function. (4) daily living essentially normal activities; and (5) no dementia. In 2004, the same authors expanded the criteria for MCI and proposed two subtypes: amnesic (which includes memory impairment) and non-amnestic (alteration of other cognitive domains).[15,16] These criteria are still valid, but including the non-amnestic type, the alteration can refer to any cognitive domain. One of the points to consider for the MCI diagnosis is that the complaint must preferably be evaluated with neuropsychological tests that corroborate the clinical information. If the evaluation determines a deficit in any cognitive function, we can determine that it is MCI. If the cognitive domain altered is memory, we will speak of amnestic type MCI if no other altered domain is found. The diagnosis of amnestic MCI, single domain, is made. If the evaluation shows that other domains (executive, visual-spatial, or language) are altered, it is called multiple-domain amnestic MCI. If memory is not affected, the clinician will determine if there is a single altered domain (single-domain non-amnestic MCI) or several altered domains (multiple-domain non-amnestic MCI).[16,17]

The DSM-5 encompasses the term major and minor Neurocognitive Disorder (NCD). These criteria are similar to those proposed by Petersen et al. The manual mentions that NCDs are cognitive alterations the individual did not present at the time, moment of birth, childhood, or adolescence, so they represent an acquired decline compared to a previous level of functioning.[18] The diagnostic criteria for the DSM-5 are as follows:

Diagnostic Criteria for Mild Neurocognitive Disorder[18]

A. Evidence of moderate cognitive decline compared to the previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor skill, or social cognition) based on:

1. Concerns may arise from the individual, a knowledgeable informant, or the clinician when there is a notable decline in a cognitive function.

2. A modest impairment in cognitive performance should ideally be documented through a standardized neuropsychological test or, if that's not possible, through another form of quantitative clinical evaluation.

B. Cognitive deficits do not hinder one's capacity to maintain independence in daily tasks. (e.g., you maintain complex instrumental activities of daily living, such as paying bills or following treatments, but you need to make higher efforts, or resort to compensation or adaptation strategies).

C. Cognitive deficits do not occur exclusively in the context of delirium.

D. Cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).[18]

The importance of timely detection of MCI lies in the fact that it has been observed that people who suffer from mild amnestic cognitive impairment tend to develop a Neurocognitive Disorder due to Alzheimer's disease.[4]

Clinical features

On the other hand, although some other mental disorders compromise cognitive performance (such as bipolar disorders or schizophrenia), the present group (TNCs) only considers those whose main characteristics refer to those of cognitive type [18,19] and whose symptomatology is explored considering the domains established in the DSM-5[18] which, depending on the clinical threshold presented, determine the diagnosis, as well as the level and specification of the subtype.[18-20]

The first domain, Complex Attention, includes the evaluation of the maintenance of attention over time (continuous attention) and with discrimination of external stimuli and distracting factors (selective attention), as well as the feasibility of carrying out two tasks in sync (divided attention). The evaluation of Executive Function is carried out taking into consideration the capacity for planning, decision making, working memory (retention of information in a short time, for manipulation), feedback (implementation to solve a problem), inhibition (ability to carry out a solution that involves greater effort) and cognitive flexibility (ability to alternate between two concepts or tasks).[18]

Regarding the learning and memory domain, immediate memory (evaluated within working memory) and recent memory (which involves encoding new information) are evaluated. In the most severe cases, semantic, autobiographical and implicit memory alterations are observed. Regarding language, the expressive capacity of the language is assessed (including the ability to name objects, through identification, fluency or phonemes), as well as grammar and syntax, and understanding of the language. Visual perception, vasoconstrictive ability (coordination of vision and manipulation of objects), perceptual-motor skills (use of movement based on perception), praxis (execution of learned movements or use of objects), and gnosis (perceptual integration of recognition and knowledge), are the subdomains belonging to the Perceptual-Motor Skills themselves.[18]

The last domain considered in the DSM-5 is Social Cognition, which encompasses emotion recognition and theory of mind (the ability to recognize experience, psyche, or other thoughts, desires, and intentions); in general, in all domains, the

significant difficulty or impossibility in carrying out these tasks on oneself, in contrast to the implication of a higher effort or notable changes in their execution, determines the severity with which the domain is compromised. As previously mentioned, the formation of this function's execution level will integrate, as appropriate, the respective diagnoses of this group of deficits.[18]

In addition to the degree of decline in the domains, the presence of apathy and, or depression in patients suffering from TNCs has been pointed out by different investigations.[20,21] These are also risk factors for developing TNCs[19] and entities related to negative consequences or worse prognoses in the progression of these deficits. Identifying these symptoms is very important and presents a challenge for clinicians. They must differentiate the symptoms effectively to implement a specialized interventions that central to managing these deficits.[20,21]

Finally, it seems relevant to mention that although the neuronal circuits involved in the development of apathy and depression in TNCs are different, a possible explanation for the presence of these symptoms is the existence of a cholinergic deficit, which is also possibly associated with other behavioral and psychological symptoms of dementia, such as irritability, agitation, psychosis, sleep disorders, anxiety, dysphoria, hallucinations, aberrant motor behavior, and delusions, such relevance and the symptoms themselves suggest being compromised by the type of deficit that has developed by the patient and its etiology.[22]

Risk factors associated with Cognitive Impairment in Older People

Risk factors in old age refer to those that accelerate the aging process and increase the chances of having MCI. These factors can be divided into two: Modifiable and non-modifiable risk factors. Among the modifiable risk factors are healthy lifestyles that affect the prevention of diseases such as diabetes, hypertension, cholesterol levels, obesity, smoking, alcohol, a sedentary lifestyle, and depression.[3]

One of the risk factors has to do with demographic aspects. After the age of 65, the risk of suffering some cognitive impairment doubles every 5 years. In terms of gender, there are no studies that reflect there is a higher prevalence in men or women. Some studies also refer to economic factors, access to health, and education issues that play a relevant role due to the cognitive reserve that people can generate throughout their lives.[4]

Non-modifiable risk factors cannot be changed, i.e., age and genetics. Some studies have shown there is a relationship between the ApoE4 genotype and cognitive impairment, and it is also associated with a higher risk of arteriosclerosis, and vascular cognitive impairment due to problems in cholesterol transport.[3]

MCI can be attributed to extrinsic factors linked to aging, for example, age-dependent diseases with cerebral repercussions such as cerebrovascular disease, hypertension, diabetes, endocrinopathies, psychiatric pathology, sociocultural isolation, and sensory alterations. There are also intrinsic individual factors, such as brain functional and structural reserve, genetic endowment, and the adaptative degree to changes during life.[3]

In MCI patients, it has been identified the presence of beta-amyloid protein and tau protein accumulation. The same as those observed in Alzheimer's disease. In other cases, there are microscopic accumulations of a protein called Lewy bodies, related to Parkinson's disease. Likewise, transient strokes or reduced blood flow through the blood vessels of the brain has been present in MCI people studies. [4]

At the brain level, neuroimaging studies allow us to observe changes in vital brain regions, i.e., a decrease in the size of the hippocampus (area involved in memory), an increase in the size of the ventricles (spaces filled with fluid in the brain), and a reduced use of glucose in the brain has also been identified. [4]

TREATMENTS FOR MILD COGNITIVE IMPAIRMENT

Pharmacotherapy

When discussing pharmacological treatment for mild cognitive impairment, it must be clear that the treatment does not aim to cure or eliminate the symptoms. The goal is to slow or stop the severity of the symptoms. The earlier pharmacological therapy starts, the course of the disease will be less aggressive than for people who start late treatment.[22]

It is relevant to clarify that the treatment mentioned below is specifically for the treatment of mild cognitive impairment due to Alzheimer's disease.

Firstly, we have Acetylcholinesterase Inhibitors (AChI), which have shown positive results in mild and moderate cognitive impairment, slowing cognitive and functional symptoms, and allowing people to maintain independence. IACh inhibit acetylcholine degradation in the synaptic cleft, allowing the drug's active substance to act more quickly and stimulate the postsynaptic receptors for longer. Among the side effects of this medication are dizziness, vomiting, nausea, diarrhea, loss of appetite, bradycardia, and urinary retention, among others.[22,23]

The most studied medications are Donepezil, Rivastigmine and Galantamine, the first has shown better results in mild and moderate cognitive impairment. However, it has not shown clinically significant results in severe stages of cognitive impairment. Donepezil's therapeutic dose is 10 mg daily before sleep in a single dose. At the beginning of treatment, only 5 mg is used, which will progressively increase to 10 mg. There are exceptional cases where the dose increases to 20 mg. However, this leads to higher side effects.[22,23]

Rivastigmine acts on the cerebral cortex, and the hippocampus bioavailability will depend on the dose. There are two ways to administer it orally and transdermally; oral administration shows gastrointestinal side effects, unlike transdermal administration which is better tolerated by patients.[24] Treatment is

individualized; however, generally starting with 3 mg, increasing the dose every three or four weeks until reaching a dose of 9-12 mg daily. Oral administration is suggested as two doses per day, with food, and in the case of the transdermal route, it is applied once a day and, as in the oral route, it begins with the lowest dose of 4.6 mg until reaching at the dose of 13.3 mg per day.[22,25]

Finally, Galantamine, which acts as a reversible acetylcholinesterase inhibitor, is administered orally twice a day. Treatment begins with 8 mg daily, increasing gradually so that at the end of the fourth week, it reaches 16 mg. The clinician will have to evaluate if there is a symptom improvement; if no therapeutic response to the drug is observed, the dose can be increased to 24 mg daily. Like the two previous medications, the most common side effects are loss of appetite, vomiting, nausea, diarrhea, abdominal pain, etc.[22,26]

Some studies have carried out clinical trials combining Donepezil and Memantine for the treatment of advanced stages of cognitive impairment of the Alzheimer type; however, they did not demonstrate clinically significant effects in any cognitive domain, functional symptoms, or caregiver overload.[24]

It is relevant to mention that in the case of older people, the way to ensure compliance with treatment is to simplify the administration regimens, reducing the number of doses per day and the administration method. It has been observed that older people requiring multiple daily doses have lower treatment adherence compared to those with fewer daily doses. [27]

PREVENTIVE MEASURES FOR MILD NEUROCOGNITIVE DISORDER

Cognitive Stimulation

According to some studies, Cognitive Stimulation (CS) is a protective factor to avoid cognitive symptoms in old age; this stimulation also impacts the cognitive reserve of the individuals. Besides having a relevant role in learning and memory processes, CS is considered one of the primary prevention strategies to avoid Neurocognitive disorder.[28]

CE denotes a collection of activities designed to preserve and improve cognitive functioning. It is achieved through exercises that address memory, attention, concentration, language, reasoning, and control. In other words, CE is a multidomain stimulation. CE is frequently carried out in a group, and training is conducted in the different cognitive domains. Generally, these types of interventions do not focus solely on a single cognitive domain, but rather, exercises or activities are multidomain. This is because people's cognitive functions are not used in isolation, and people are constantly interacting in the indivudual's daily lives. [3,4]

CE is used to prevent cognitive deterioration and not as a rehabilitation tool. It aims at either preserving or improving the cognitive functioning of the different cognitive domains of older people.[28] For Madrigal, CE should enhance cognitive functioning in older people in such a way that they have a positive impact on their life quality. For this reason, interventions must compensate and promote adaptation in the social environment where older people interact.[29] Just as two cognitive domains relate, cognition and affectivity also go hand in hand, which is why an improvement in mood has been noted in patients who receive some cognitive training.[30]

In a systematic review study carried out in 2017, articles from 2001 to 2017 were reviewed; from the studies reviewed, 98% had positive results and obtained an increase in cognitive capacity, increasing the independence and quality of life of older adults.[31] The studies presented vary the application time of cognitive stimulation, on average the time is between 7 and 12 weeks, i.e., from two to 4 months. Besides, 30 studies performed cross-sectional studies. Therefore, conducting this study enhances older people's autonomy and quality of life.[32]

Transcranial Direct Current Stimulation in the Treatment of Mild Cognitive Impairment

Recently, work has begun using neuromodulation techniques, which depolarize the neuron. This depolarization is carried out by passing low-intensity electrical impulses, resulting in the excitation or inhibition of the neuron. Among the neuromodulation techniques currently used is transcranial direct current stimulation (tDCS), which has been used to treat psychiatric and neurocognitive conditions. Non-invasive techniques involve applying low electrical impulses (typically between 0.5 and 2 mA) through two electrodes with positive and negative charges positioned on the scalp. These electrodes allow the passage of direct and constant electrical current. The electric current penetrates the cerebral cortex, reaching the cortical and subcortical layers, having an expiatory response from the neuron, increasing neuronal plasticity.[33]

Within the literature, different randomized clinical show the benefits of using tDCS, such as Murugaraja et al.[34] where the results show that tDCS is safe and potentially beneficial in combating cognitive deficits in patients with mild cognitive impairment. Another randomized, double-blind clinical trial in older adults with MCI and who underwent tDCS has shown that it can significantly improve executive function in MoCA and performance in Trail Making Test Version A and B (TMT-A/B).[32] Likewise, tDCS has been shown to improve visual sustained attention, spatial WM, and visual memory as assessed using digital neuropsychological tests.[34,35]

According to the evidence reviewed, tDSC is considered a safe technique.[36] Different clinical trials reported mild adverse effects, such as itching, burning or tingling at the application site and headache and fatigue during or minutes after. There are several factors that increase the risk of local side effects, such as high skin impedance, small and dry electrodes, incorrect electrode placement, contact with the skin, and allergic predisposition.[37]

Among the various tDCS studies conducted are the ones performed by Manor et al.[37] They conducted randomized, double-blind clinical trials on older adults with MCI who also underwent tDCS. The trials demonstrated that tDCS can significantly improve executive function as measured by MoCA and performance in Trail Making Test Version A and B (TMT-A/B).[38]

CONCLUSIONS

Although the results of the different investigations indeed demonstrate that both CE and tDCS are efficient in preventing some main cognitive alterations, we must mention that the objective of both CE and tDCS is not curative, and that its effectiveness is measured by the reduction of mild symptoms or by the fact that it does not progress to more severe stages. According to a recent systematic review conducted by da Silva et al., the tDCS+CT combination does not seem to enhance the effects of tDCS basically due to the variability of protocols.[36] The above represents a challenge to verify whether there is a significant benefit from the synergistic application of two stimulation interventions to treat MCI, whether cognitive interventions and neuromodulation techniques, or interventions that contemplate three types of intervention to evaluate the efficacy and effectiveness of the treatments together.

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