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EDITORIAL

Neurological disease and behavioral changes in the human being

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It is well known that the prominent expression of the work of our brain is behavior, understood as the combination of a structure that expresses a function that is the result of the acquisition of learning overtime of experiences and purchase of skills.

Human behavior is intriguing because each individual expresses it differently, as is the facial expression or the fingerprint.

Behavior is the result of a history written overtime in our genes, a cortical mat growing to fold and forming grooves to be contained in a firm and immovable structure that is the skull.

It is capable of perceiving different stimuli in areas specifically assigned to it. Moreover, it can generate specific responses that originate in phrenologically selected areas but interact in an incredible way to connect with the primitive systems that we maintain in the brain stem and jointly explain genius and the impulsivity that explains a horrible decision unreasoned response.

The human being who achieves a balance in his life is the one who is productive for himself, his family, and society. Possibly happy is the one who manages to passionately love his family and work, combining in everyday life the ability to value what he has and enjoys it. If envy comes, it should be only to force us to surpass ourselves.

However, we live in a society where each individual has his ideas and value judgments. Some understand that self-improvement, justice, honesty, and equity are necessary and desirable values in a society that can continue to improve. However, unfortunately, some see themselves as superior beings who can dominate, manipulate, influence, or even take the lives of others.

Social interaction is already complex due to the characteristics of each individual. Their genetic program, their life experiences, their level of education, their purchasing power make the behavior of human beings a complex expression to evaluate for psychologists, psychiatrists, neurosurgeons, or neurologists, even considering only the biological aspect. This problem is not only for us as physicians; we can either mention philosophers, sociologists, and even politicians.

We have all lived the experience as physicians of a patient with a degenerative disease who went, from being demure, to becoming a verbose, cursing, inopportune, uninhibited, hypersexual, sometimes funny, but at other times extremely reckless individual.

We have also witnessed the false but credible stories for the family of "your brother stole from me, hid from me, took away, took the money you gave me." And that behavior provokes disastrous intrafamily conflicts because the family was not yet aware of the neurodegenerative problem that their relative was beginning to show.

The clingy, dependent, manipulative, absorbing, advantageous behavior that the patient with epilepsy can take; the negligence, the ignorance left-right, the agnosia for faces that can provoke a stroke.

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We have also seen the lack of vital impulse, the onset of movement, loss of spontaneity, and affective flattening that can be seen in a bifrontal lesion.

All of this make the analysis of behavior and the determination of normality or abnormality very complex.

We all may have a certain degree of mental illness. And it indeed does no one any harm to have a behavioral evaluation because whether we like it or not, we all must get sick with something just as we will die for some reason.

Those of us who assess brain disease should constantly strive to maintain proper behavior in a complicated society and be aware of the risk we will always face of suffering from brain disease.

"In our case, in order to *give* we will always have to *have* health."

In the meantime, if we can enjoy reading and continue to learn about our brains and the brains of others, let us love with passion not only our family but also the fantastic job we have been given in society as health-care providers. Let us perform the miracles that we are called to serve, thanks to the knowledge and skills that we have acquired throughout our training, and let us infect others to follow this exciting path of neurosciences.

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ORIGINAL ARTICLE

Lissencephaly: Clinical and neuroimaging features in children

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Abstract

Background: *The spectrum of lissencephaly (LIS) corresponds to a group of serious brain malformations in the cortex caused by a failure in neuronal migration. The spectrum includes agyria, pachygyria and subcortical band heterotopia (SBH). It has generally been divided into two categories: classic lissencephaly or type I, and cobblestone lissencephaly or type II.* **Objective:** *The objective of the study was to describe clinical, neuroimaging, and neurophysiological features of pediatric patients with lissencephaly (LIS) type I.* **Methods:** *Retrospective study of children with the diagnosis of LIS, who were admitted to the National Institute of Pediatrics in Mexico City from January 2009 to December 2019.* **Results:** *We included a total of 22 patients, 15 (68%) were male. Age at diagnosis: 4 (18%) children under 1 month due to ventricular dilation on ultrasound and epileptic spasms; 13 (59%) children of 1 month-1 year due to microcephaly, drug-resistant epilepsy, and neurodevelopmental delay; 5 (22%) children over 1 year. Regarding etiology: 6 cases were due to cytomegalovirus, 1 to Zika, and 1 to microdeletion diagnosed as Miller-Dieker syndrome. All (100%) had neurodevelopmental delay, 19 (86%) intellectual disability. Epilepsy was found in 19 (86%), of these 6 had epileptic spasms, 7 had West syndrome, and 5 evolved to Lennox-Gastaut. Drug-resistant epilepsy was present in 17 (77%) patients. Regarding comorbidities: 15 (68%) had gastroesophageal reflux disease and 14 (63%) had recurrent pneumonia. Regarding neuroimaging findings, paquigiria was present in 9 (41%) children. Two children died, they had diffuse agyria.* **Conclusions:** *LIS type I includes pathologies with a poor prognosis, manifested predominantly in the 1st year of life. All patients have delayed psychomotor development, refractory epilepsy and were associated with different comorbidities. Genetic and neuroimaging studies are important to make an accurate diagnosis, predict evolution, offer genetic counseling, and palliative treatment.*

Key words: *Lissencephaly. Pachygyria. Agyria. Children.*

Lisencefalia: características clínicas y de neuroimagen en niños

Resumen

Antecedentes: *El espectro de lisencefalia (LIS) corresponde a un grupo de graves malformaciones cerebrales en la corteza causadas por un fallo en la migración neuronal. El espectro incluye agiria, paquigiria y heterotopía de banda subcortical (SBH). Generalmente se ha dividido en dos categorías: lisencefalia clásica o tipo I y lisencefalia en empedrado o tipo II.* **Objetivo:** *Describir las características clínicas, neuroimagen y neurofisiológicas de pacientes pediátricos con Lisencefalia tipo I.* **Métodos:** *Estudio retrospectivo y descriptivo de pacientes con diagnóstico de lisencefalia atendidos en el Servicio de Neurología Pediátrica del Instituto Nacional de Pediatría, en la Ciudad de México, de enero de 2009 a diciembre de 2019.* **Resultados:** *Incluimos un total de 22 pacientes, 15 (68%) eran hombres. Edad al diagnóstico: período neonatal 4 (18%) por*

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dilatación ventricular en ultrasonido, Zika materno y espasmos epilépticos; de 1 mes a 1 año: 13 (59%) por microcefalia, epilepsia fármaco resistente y retraso del neurodesarrollo y mayores de 1 año: 5 (22%) niños. Etiología: 6 por Citomegalovirus, 1 por Zika y 1 microdeleción con síndrome de Miller Dieker. Todos tuvieron retraso del neurodesarrollo, 19 con discapacidad intelectual (3 pacientes < 4 años). Epilepsia en 19 (86%), 6 tuvieron espasmos epilépticos, 7 Síndrome de West, 5 evolucionaron a Lennox Gastaut. Epilepsia fármaco resistente en 17 (77%). Comorbilidades: 14 (63%) neumonías a repetición y 15 (68%) con enfermedad por reflujo gastroesofágico. Paquigiria en 9 (41%) niños. Dos niños murieron, tenían agiria difusa. **Conclusión:** *Lisencefalia tipo I incluye patologías de mal pronóstico, que se manifiesta predominantemente en el primer año de vida. Todos los pacientes tienen retraso en el desarrollo psicomotor, epilepsia refractaria y se asocian a diferentes comorbilidades. Es importante el estudio genético y neuroimagen de alta resolución para realizar un diagnóstico preciso, predecir evolución, ofrecer consejo genético y tratamiento paliativo.*

Palabras clave: *Lisencefalia. Paquigiria. Agiria. Niños*

Introduction

The spectrum of lissencephaly (LIS) corresponds to a group of serious brain malformations caused by a failure in neuronal migration. LIS, a term introduced by Owen Richard in 1868, comes from the Greek words "lissos" means smooth or soft and "enkephalos" means brain, it is a descriptive term. This term applied to malformations with abnormal formation of the cerebral convolutions, characterized by a smooth brain surface, intellectual disability, and seizures[1,2].

The spectrum of LIS includes agyria (complete absence of cerebral convolutions), pachygyria (from the Greek "paqui" (παχύς) means thick or broad, it is a malformation with wide cerebral gyri)[3-5], and subcortical band heterotopia (SBH) (also called double cortex, consists of smooth layers of gray matter that frequently follow the curvature of the overlying cortex)[6].

There are several forms of classification, but the most used is type I and type II LIS[7]. Type I or classic LIS in which it has four cell layers in the cortex, it can present in two forms such as isolated LIS and Miller-Dieker syndrome (MDS)[8]. Type II or cobblestone LIS in which the cerebral cortex is highly unstructured presents in three syndromes: Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy[9,10].

Osborn et al.[11] estimated that the prevalence of LIS is approximately 1-4:100,000 newborns. Three genes are associated with classical LIS: LIS1, doublecortin (DCX), and TUBA1A[12]. Likewise, some studies report association with viral infections.

Clinically, infants present marked psychomotor developmental delay, severe epileptic encephalopathy drug refractory, and some cases facial dysmorphias associated a specific genetic syndromes[13]. Magnetic resonance imaging (MRI) has become an important supplement evaluation and classification.

Although the overall incidence of LIS is rare, its comorbidities are serious, affecting neurodevelopment, causing a degree of disability, and impairing their quality of life and vital prognosis. The aim of our study was to describe clinical, neuroimaging, and neurophysiological features of pediatric patients with LIS type I attended at the National Institute of Pediatrics in Mexico City.

Methods

This was a single-center retrospective study of pediatric patients (< 18 years) with a diagnosis of LIS admitted to the National Pediatrics Institute from January 2009 to July 2019. We included patients with MRI showing structural alteration of the cerebral cortex compatible with the classic LIS included SBH and patients with sufficient clinical information and electroencephalograms (EEG) to be classified as LIS, patients with electroencephalograms (EEG) to be classified as LIS type I, and patients with sufficient clinical information. We excluded patients with another abnormal neuronal migration such as: cobblestone LIS, complex or congenital muscular dystrophy and schizencephaly, or with incomplete information in medical records. The local ethics committee approved this protocol.

We recorded demographic and clinical data as well imaging, genetic, and neurophysiological studies of the patients. Epileptic seizures were classified according to the International League Against Epilepsy 2017 guidelines. Drug-resistant epilepsy was defined as seizures occurring despite the use of two antiepileptic drugs (AEDs) at appropriate doses.

EEG patterns were classified according to the patterns described by Hakamada et al.[14], recognized since 1979. This classification shows three unique EEG patterns: Grades I, II, and III.

The features observed in brain MRI were classified using the Grading System for Classical LIS and SBH, modified by Dobyns[15]. This system grades the

Table 1. Grading system for classic lissencephaly and SBH

Grade	Description of cortical malformation	Gradient	
1	Diffuse agyria		1a = p*
2	Diffuse agyria with a few shallow sulci	2a: over frontal and temporal poles 2b: over occipital poles	2p > a 2a > p
3	Mixed agyria and pachygyria	3a: frontal pachygyria and posterior agyria 3b: frontal agyria and posterior pachygyria	3p > a 3a > p
4	Diffuse or partial pachygyria only	4a: greater posterior than anterior pachygyria 4b: greater anterior than posterior pachygyria	4p > a 4a > p
5	Mixed pachygyria and SBH	5a: frontal SBH and posterior pachygyria 5b: frontal pachygyria and posterior SBH	5p > a** 5a > p
6	Subcortical band heterotopia only	6a: SBH posterior predominance 6b: SBH anterior predominance	6p > a 6a > p

Modified from Dobyns and Truwit (1995)[15]. Grades 1–6 denote the overall severity of the lissencephaly seen on neuroimaging. P > a means more severe posteriorly. a > p means more severe anteriorly.
* With severe Grade 1 lissencephaly, it is difficult to determine if a gradient is present.
**The reverse (5p > a) has not been observed.
SBH: subcortical band heterotopia.

Table 2. Clinical and paraclinical features of children with lissencephaly

Variable	n = 22
Age (years), median (range)	9.3 (3-16)
Sex	
Male, n (%)	15 (68)
Female, n (%)	7 (32)
Age at onset	
< 1 month old, n (%)	4 (18)
1 month-1 year old, n (%)	13 (59)
Older than 1 year old, n (%)	5 (22)
History of	
Epilepsy, n (%)	8 (36)
Threatened abortion, n (%)	7 (31)
Consanguinity, n (%)	3 (13)
Etiology	
Unidentified, n (%)	14 (64)
Cytomegalovirus, n (%)	6 (27)
Zika, n (%)	1 (4.5)
Microdeletion, n (%)	1 (4.5)
Clinical findings	
Neurodevelopmental delay, n (%)	22 (100)
Intellectual disability, n (%)	19 (86)
Epilepsy, n (%)	19 (86)
Hypertonia, n (%)	18 (81)
Microcephaly, n (%)	15 (68)
Low weight for age, n (%)	14 (63)
Facial dysmorphism, n (%)	11 (50)
Spastic quadriparesis, n (%)	8 (36)
Hypotonia, n (%)	4 (18)
Macrocephaly, n (%)	2 (9)
Miller-Dieker syndrome, n (%)	1 (4.5)
Genetic studies	
Normal karyotype, n (%)	13 (59)
Normal FISH study 17p13.3 (LIS1 locus), n (%)	6 (27)
Microdeletion in FISH study 17p13.3 (LIS1 locus), n (%)	1 (5)

FISH: fluorescence *in situ* hybridization.

neuroradiological appearance of LIS in 6-level based on the severity and anterior-posterior gradient of the abnormalities, from severe Grade 1 (complete agyria) to mild Grade 6 (SBH only) (Table 1).

We used descriptive statistics, frequencies and proportions were calculated for categorical data, and measures of central tendency (mean) were calculated for continuous data.

Results

A total of 22 patients with LIS type 1 were included. Fifteen were male (68%) and 7 females (32%). Their mean age was 9.3 years with a range of 3-16 years of age. Two patients died at the 4th and 5th years of age, respectively, due to pneumonia. Regarding genetic studies, 13 (59%) children had a normal karyotype of these only seven children were realized the test fluorescence *in situ* hybridization (FISH). Only one child was found with microdeletions of chromosome 17p13.3, this was diagnosed with MDS. Of the total of patients, only seven patients had toxoplasma, rubella, cytomegalovirus (CMV) and herpes simplex virus (TORCH) profile test and of these six were positive for CMV (Table 2).

Regarding clinical presentation symptoms in table 2, neurodevelopmental delay was present in all patients. Intellectual disability was reported in 19 (86%) children,

Table 3. Epilepsy features and EEG patterns in children with lissencephaly

Variable	n = 22
Age at epilepsy onset	
Age (month), median (range)	8 months (7 days-2 years)
Epileptic syndromes	
West syndrome, n (%)	6 (32)
Lennox-Gastaut syndrome, n (%)	5 (26)
Non-syndromic epilepsy	
Epileptic spasms, n (%)	6 (32)
Focal motor seizures, n (%)	7 (37)
Generalized tonic-clonic seizure, n (%)	6 (32)
Epileptic status	10 (52)
Drug-resistant epilepsy	17 (89%)
EEG patterns	
Grade I, n (%)	8 (42)
Grade II, n (%)	6 (32)
Grade III, n (%)	5 (31)
Other EEG findings	
Generalized background slowing, n (%)	15 (78)
Asymmetric pattern, n (%)	3 (15)
Hypsarrhythmia, n (%-)	6 (32)
Burst suppression, n (%)	1 (4)
Generalized spike-slow wave discharges of 1.5-2.5 Hz, n (%)	5 (31)

EEG: electroencephalogram.

this due to three patients was under 5 years of age and could not be classified that way. Intellectual disability was determined using the Wechsler Intelligence Scale in Children-IV 2003 for children of 6-16 years. Mild intellectual disability was found in 6 (27%), moderate in 3 (14%), severe in 8 (36%), and deep in 2 (9%) children. Facial dysmorphia was founded in 11 (50%) patients, among the findings were downward oblique palpebral fissures, epicanthus, long philtrum, hypertelorism, depressed nasal bridge, and high palate. Other findings not discussed in table 2 were clinodactyly, strabismus, cryptorchidism, scoliosis, clubfoot, and valgus foot. We founded that the four children with hypotonia in the 1st year, later developed hypertonia with spasticity of the limbs.

Of the 22 patients in the study, 19 (86%) had electroclinical seizures. The most frequently reported epileptic syndrome was West syndrome in 6 (32%) children and of these 5 evolved to Lennox-Gastaut syndrome (Table 3).

The three EEG patterns of LIS described by Hakamada et al.[14] are described as follows: Grade I, diffuse bi-hemispheric distribution of a mixture of high-amplitude alpha (8 Hz) and beta (14-16 Hz) activity 100-200 μV; Grade II, diffuse bi-hemispheric distribution of slow waves from 1.5 to 2.5 Hz with high-amplitude acute waves up to 300 μV, associated with short periods of attenuation of cortical activity lasting up to 3 s in duration; and Grade III generalized activity with acute 1-1.5 Hz high-amplitude waves of 400 μV. We found that the 19 children had at least one of the three EEG patterns. Other electroencephalographic findings were background patterns with generalized slow activity in 15 (78%) patients (Table 3). In all our patients, the amplitude during wakefulness ranged from 100 to 350 mV, with occasional high-amplitude discharges of up to 500 mV.

According to the classification system for LIS modified by Dobyns[15], in brain MRI, the most frequent was Grade 4 correspond to pachygyria in 9 (41%) children. We founded predominance of anteroposterior gradient (more severe lesion anterior). Furthermore, we found 4 (18%) children in Grade 2, agyria with undulation of brain cortex; 3 (14%) children in Grade 1, diffuse agyria; 3 (14%) children in Grade 3, mixed agyria and pachygyria; 2 (9%) children in Grade 5, pachygyria and SBH; and only 1 (4.5%) child in Grade 6, SBH. The two patients who died had diffuse agyria this is the most severe form. Other findings in brain MRI were agenesis of the corpus callosum, polymicrogyria, and cisterna magna (Figs. 1 and 2).

Regarding other neuroimaging studies, we founded 12 patients who had a brain computed tomography (CT), 8 patients who had a prenatal ultrasound, and 2 patients with transfontanellar ultrasound. In the brain CT studies, reports of thick cortical gyrus were founded in five children, cortical atrophy in four children, and ventriculomegaly in two children. In the prenatal ultrasound studies, reports of intrauterine growth restriction were found in four children, ventricular dilation in a single child, and in three children, the report was normal. The two children who underwent transfontanellar ultrasound were both reported with ventriculomegaly.

Regarding comorbidities, the most common was gastroesophageal reflux disease in 15 (68%) patients and of these 10 patients underwent Nissen fundoplication and gastrostomy. Other comorbidities founded were recurrent pneumonia in 14 (63%) patients, heart disease (ventricular septal defect and ductus arteriosus) reported in two children, intestinal atresia in one, and hypothyroidism in another.

Discussion

There are no exact data on the prevalence of LIS, however, studies report the overall incidence is 1 in 100,000 live births or even higher, up to 1 in 13,000-20,000 live births[16]. The Royal Children's Hospital in Melbourne reported 2-4 new patients with classic LIS per year, which is equivalent to an incidence of

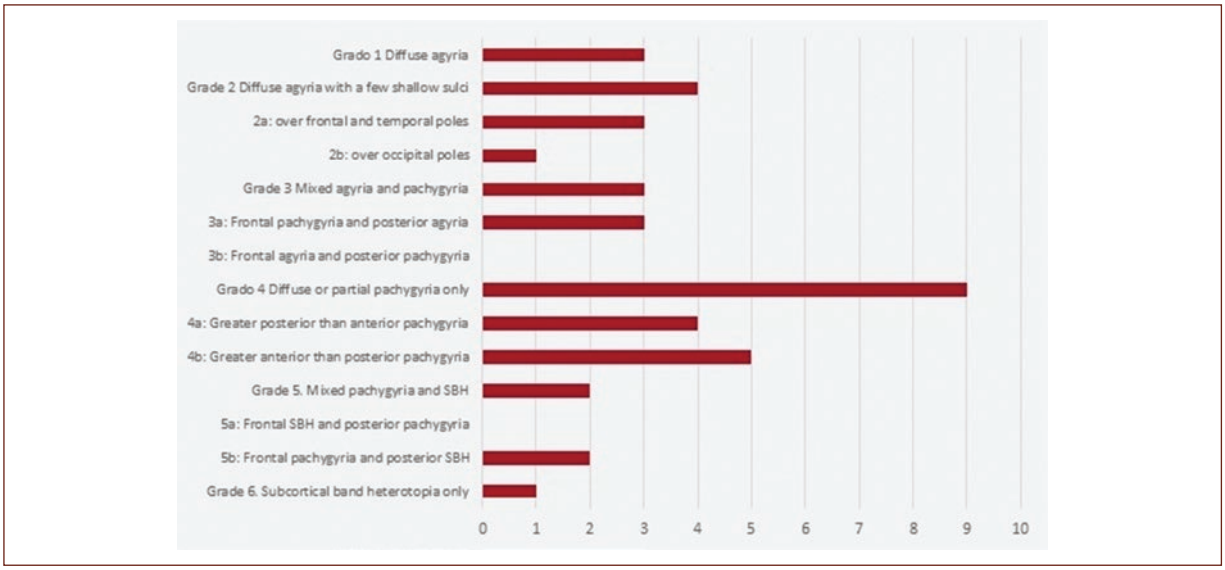

Figure 1. Classification of the brain MRI findings of children with lissencephaly according to grading system for classic lissencephaly and SBH. SBH: subcortical band heterotopia.

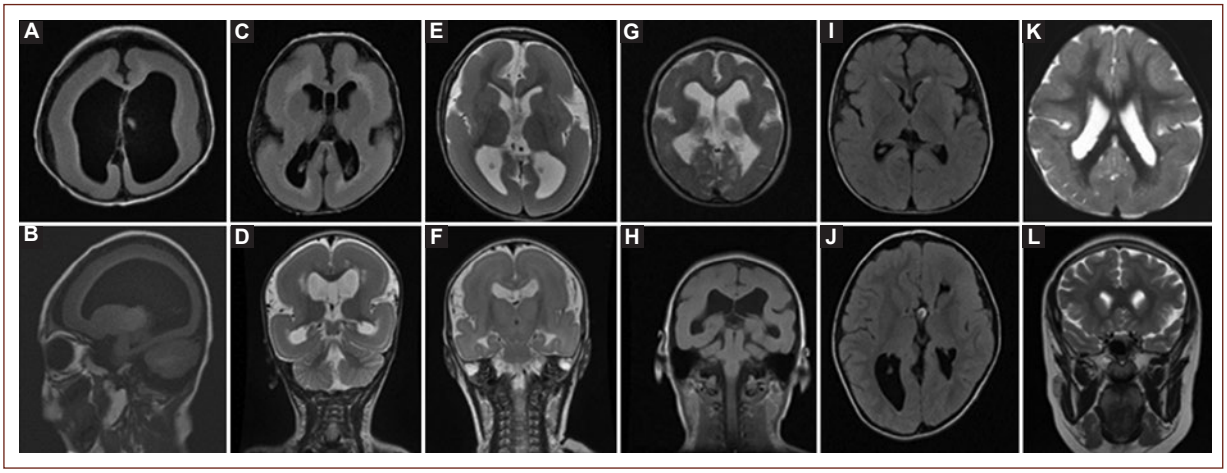

Figure 2. Brain MRI findings. **A and B:** agyria diffuse. **C-F:** agyria diffuse with few superficial undulations on frontal and temporal poles. **G-H:** agyria and pachygyria mixed, with frontal pachygyria and parieto-occipital agyria. **I-J:** partial pachygyria more severe anterior. **K:** more severe partial pachygyria posterior. **L:** heterotopia in subcortical band.

approximately 1:25,000 live births[11]. In our study, we reviewed clinical records in the last 10 years and we found 22 patients with classic LIS, which represents approximately 2.2 cases per year.

The cause of LIS is unknown but probably heterogeneous[5]. In about 80% of cases of classical LIS, a genetic cause can be found, usually an abnormality of the LIS1 or DCX gene[17]. In our medium, the genetic study is limited to performing a karyogram and FISH for chromosome 17, probably due to the cost of genetic tests.

In our study, only one patient was diagnosed with MDS[18] determined by a microdeletion spanning the gene LIS1 at chromosome 17p13.3. This patient was a male of 4 years old. He presented distinctive facial features (prominent forehead, bitemporal narrowing, midface hypoplasia, upturned nares, protuberant upper lip, low seat ears, and micrognathia), as well as heart disease (interatrial communication), gastroesophageal reflux disease, and epileptic spasms.

We were looking for a history of ingestion or exposure to drugs or toxins during pregnancy, but these data were not reported.

LIS has been associated with intrauterine viral infection, CMV is the most frequent. Early second-trimester CMV infection leads to LIS, while late second-trimester infection causes polymicrogyria[19]. Other pathogens involved are toxoplasmosis, rubella, herpes simplex, human immunodeficiency virus, and syphilis. In a review in Australia of 12 children with cerebral palsy and congenital CMV, the children had epilepsy, intellectual deficit and the brain malformations found were LIS, pachygyria, polymicrogyria, cerebellar hypoplasia, ventricular dilatation, and calcifications[20]. In our study, more than half of the patients did not have a TORCH profile test and are unknown whether there is an association with these viruses.

We report a patient who had a diagnosis of prenatal Zika infection. The patient was a girl of 2 years old. She also had microcephaly[21]. Her diagnosis could be determined because her mother underwent the Zika test as a screening, her mother was from Chiapas State.

Our findings show the same clinical manifestations reported in the Dobyns[5] study in 1990 and 2010 categorized as (1) neurological deficits, poor feeding, hypotonia, and opisthotonos; (2) delayed neurodevelopment; or (3) seizures[13,22,23].

Studies report that the frequency of epilepsy in children with LIS could be 35-85% or up to 90% this number is like those found in our study[5,23]. The onset of epilepsy is early usually between 3 and 12 months[5], in our study, the average was 8 months. Children with LIS present several types of epilepsy. Epileptic spasms are the most frequent up to 80%, which often progress to West syndrome and Lennox-Gastaut syndrome[24]. Focal motor seizures (myoclonic, tonic, and atonic), atypical absences, and generalized tonic-clonic seizure are also observed[24]. Drug-resistant epilepsy can be an independent factor contributing to mental retardation, developmental delay, and eating problems. In classical LIS, studies in mutated mice have shown specific deficiencies in cortical interneurons that use γ-aminobutyric acid (GABA) as neurotransmitter[25]. Therefore, GABAergic AEDs could be used. However, there is currently no FAE recommended as the gold standard in treatment.[24,25].

As previously mentioned, Hakamada et al.[14] determined three specific EEG patterns in LIS. Ferrier et al.[26] suggested that these EEG changes may be due to the lack of sulci and denervation super sensitivity of the abnormal neurons, picked up by scalp electrodes. Gastaut et al.[27] proposed that the rhythmicity and increased amplitude were related to the abnormal organization and orientation of these cortical layers.

Pattern I EEG of high-amplitude fast activity of alpha frequency intermixed with beta is most characteristic of LIS[28]. Jauhari et al.[29] reported that EEG pattern recognition aids in diagnosis of LIS. EEG pattern III is associated with severe developmental delay and drug-resistant epilepsy. In this study with 28 children, the EEG pattern I was the most common 14 (50%)[29]. In our study, the EEG pattern I also was the most common in 8 (42%) children.

Many children with LIS have bulbar difficulties that result in difficulties with feeding and respiratory function[23], as reported in our research, the most frequent comorbidities were gastroesophageal reflux and recurrent pneumonia. Furthermore, there are reports of various non-neurological abnormalities such as congenital heart disease, cataracts, duodenal atresia, renal agenesis, polydactyly or syndactyly, and cryptorchidism[30].

Prenatal diagnosis of LIS, although difficult, can be suspected from 23 weeks of gestation. The abnormal features in prenatal US images at 23 weeks are ventriculomegaly and shallow Sylvian fissure[31]. In older gestational ages, other findings are widespread agyria, abnormal insula, corpus callosum, microcephaly, intrauterine growth restriction, and hydramnios[32].

Dobyns et al.[15] observed two types of patterns or gradient of severity according to brain MRI imaging findings. The first pattern is an anteroposterior gradient (a > p) with greater involvement in the anterior cerebral cortex (frontal lobe). The second pattern is a posteroanterior gradient (p > a) with greater involvement in the posterior cerebral cortex (parietal or occipital lobe)[5,15]. In the most severe form of LIS (complete agyria), can be difficult to differentiate the type of pattern. Di Donato et al.[22] reported that the most common form of LIS was partial agyria-pachygyria that was most severe posteriorly (posteroanterior gradient) or Grade 3a (3p > a). In our study, only three children have this grade. The next most common patterns were pachygyria[22]. In our review, pachygyria (grade 4) was the most common.

Treatment is generally symptomatic and supportive[33]. The most patients used antiepileptic polytherapy that was ineffective. As previously mentioned, a large percentage of patient required gastrostomy, several had multiple hospitalizations for status epilepticus and pneumonia. Children with heart disease received cardiology treatment and some children required orthopedic management and surgery.

The prognosis depends on the severity of the malformations, some forms of LIS have a severe neurological phenotype with a markedly reduced life expectancy

and many dies before the age of 10 years[33]. For classic LIS, the mortality rate is > 50% at 10 years and few children live more than 20 years[5,34]. Respiratory diseases are the most common causes of comorbidities and death[35]. In our study, the two patients died due pneumonia and both had diffuse agyria.

Conclusions

LIS includes pathologies with a poor prognosis, manifested predominantly in the 1st year of life. Neurodevelopmental cognitive and motor alterations are frequent and significant. All patients with LIS have neurodevelopmental delay, drug-resistant epilepsy and are associated with different comorbidities. The pattern most frequent in EEG is Grade I. In brain MRI, pachygyria is the malformation most frequent. An early diagnosis can be made with an adequate prenatal ultrasound. Our suggestions are: to recognize EEG patterns in LIS and clinical findings to facilitate the diagnosis; To consider the types of patterns or gradient of severity according to brain MRI imaging findings as a prognostic factor; To research etiology with genetic studies and testing for viral infections, (and in addition, offering genetic counseling); Diagnosing and initiating symptomatic treatment in early stages to avoid comorbidities. Finally, more studies are required to better understand and improve the treatment and outcome of this pathology.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Split hand phenomenon: An early marker for amyotrophic lateral sclerosis

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Abstract

Background: *Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by degeneration of upper and lower motor neurons. Time from symptom onset to confirmed diagnosis has been reported from 8 to 15 months in ALS.* **Objectives:** *To describe the frequency of the split hand phenomenon and propose it as an early biomarker for ALS diagnosis.* **Methods:** *A retrospective, analytical, descriptive, and single-center observational study was performed. The split hand ratio was determined by dividing distal abductor pollicis brevis/abductor digit minimi compound muscle action potentials; a result < 0.6 was considered present.* **Results:** *Fifty-four patients with ALS diagnosis were included in the study. The split hand ratio was identified in 61.5% of patients with definite ALS, in 68.7% with probable ALS, 80% with possible ALS, and in 50% with suspected ALS. The split hand phenomenon was identified in 60% of patients within 12 months of symptom onset.* **Conclusion:** *We provide evidence for an additional neurophysiological tool that helps early diagnosis of ALS.*

Key words: *Amyotrophic lateral sclerosis. Motor neuron disease. Split hand phenomenon. El Escorial criteria.*

Fenómeno de mano dividida: Un marcador temprano de esclerosis lateral amiotrófica

Resumen

Antecedentes: *La esclerosis lateral amiotrófica (ELA) es una enfermedad progresiva caracterizada por la degeneración de las neuronas motoras superiores e inferiores. Se ha reportado que el tiempo desde el inicio de los síntomas hasta el diagnóstico confirmado es de 8 a 15 meses.* **Objetivo:** *Describir la frecuencia del fenómeno de mano dividida en las etapas iniciales de la enfermedad y proponerlo como un marcador temprano para el diagnóstico.* **Métodos:** *se realizó un estudio observacional retrospectivo, analítico, descriptivo y unicéntrico. La relación de mano dividida se determinó dividiendo los potenciales de acción compuestos motores distales entre abductor pollicis brevis/abductor digit minimi (APB/ADM); se consideró presente un resultado <0.6.* **Resultados:** *Se incluyeron cincuenta y cuatro pacientes con diagnóstico de ELA. El fenómeno de mano dividida se identificó en el 61.5% de los pacientes con ELA definida, en el 68.7% con ELA probable, el 80% con ELA posible y en el 50% con sospecha de ELA. El fenómeno de la mano dividida se identificó en el 60% de los pacientes dentro de los primeros 12 meses tras el inicio de síntomas.* **Conclusión:** *Proporcionamos evidencia para una herramienta neurofisiológica en la ayuda del diagnóstico temprano de ELA.*

Palabras clave: *Esclerosis lateral amiotrófica. Enfermedad de la motoneurona. Fenómeno de mano dividida. El Escorial criteria.*

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs), leading to gradual weakness that affects bulbar, cervical, thoracic, and lumbar muscles[1]. Diagnosis is based on clinical and neurophysiological findings, and currently, there are no biomarkers or additional tools to rely on[2]. To date, pathophysiological mechanisms are not fully understood, however, it is widely assumed that ALS is the result of an interaction between genetic and environmental factors[3].

Time from symptom onset to confirmed diagnosis has been reported from 8 to 15 months in ALS[4]. About half of patients receive at least one alternative diagnosis before diagnostic confirmation. This delay in diagnosis represents a missed opportunity to prompt research and address the patient's symptoms[5].

The split hand sign denotes localized weakness and wasting of the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles with relative sparing of the abductor digit minimi (ADM)[6]. In nerve conduction studies (NCSs), a decreased APB/ADM compound muscle action potential (CMAP) amplitude ratio (< 0.6) reflects the split hand phenomenon, which in ALS indicates cortical motor neuron compromise, particularly because APB and FDI are muscles with extensive corticospinal connections affected by glutamate excitotoxicity[7]. The split hand phenomenon is observed in 55% of ALS patients. The dissociated hand muscle atrophy, particularly the combination of APB/ADM ratio < 0.6 and FDI/ADM ratio < 0.9, is rarely found in pure LMN disease, cervical spondylotic amyotrophy, and polyneuropathies[8]. As few data exist on split hand ratio in patients with ALS, we aim to describe the frequency of this phenomenon in the early stages of the disease.

Methods

A retrospective, analytical, descriptive, and single-center observational study was performed in the period from January 2017 to December 2019. Patients diagnosed with any degree of certainty of ALS (suspected, possible, probable, and definitive) by "El Escorial" were included in the study. ALS patients aged at least 18 years with complete NCSs were enrolled. Patients with incomplete medical records were excluded, as well as those with cervical spondylotic myelopathy, peripheral neuropathies, and pure LMN disease.

NCSs were performed by a neurophysiologist with extensive experience in neuromuscular diseases. The distal CMAP (mV) recordings were obtained from the median (stimulating in the elbow with recording in the APB muscle) and ulnar nerves (stimulating in the elbow with recording in the adductor digiti minimi muscle). The split hand ratio was determined by dividing distal APB/ADM CMAPs; a result < 0.6 was considered present.

We defined ALS stages according to time. Early-stage ALS was defined as < 12 months since symptom onset. On the other hand, late stage was considered if symptoms have more than 12 months.

Statistical analysis

For descriptive analysis, data distribution was determined with Kolmogorov–Smirnov test. Variables were described as mean, ± standard deviation, or median and interquartile range according to distribution. Categorical variables were described in frequencies and percentages. The ANOVA test for continuous parametric variables was used to search for differences between groups. Mann–Whitney U-test was used for non-parametric continuous variables, as well as the Chi-square test and Fisher's exact test for categorical variables. $p \leq 0.05$ was considered statistically significant.

Results

Fifty-four patients with ALS diagnosis were included in the study. About 52% were men and the mean age at diagnosis was 52.8 ± 11.4 years. Median time from symptom onset to diagnosis was 24 months. Considering the different degrees of diagnostic certainty of ALS according to the El Escorial criteria, 48.1% fulfilled criteria for defined ALS, 29.6% for probable ALS, 18.5% for possible ALS, and 3.6% for suspected ALS. Patients with definite, probable, and possible ALS had a shorter time from symptom onset to diagnosis with a mean of 24 months, compared to 60 months in the suspected ALS group (Table 1). Patients with definite, probable, and possible ALS had earlier NCS performed, contrarily to those with suspected ALS (55.5 months).

The split hand ratio could not be calculated in 5% of patients due to unexcitable nerves. The split hand phenomenon was identified in 70% of ALS patients. Regarding the degree of certainty of the El Escorial criteria, the split hand ratio was identified in 61.5% of patients with definite ALS, in 68.7% with probable ALS,

Table 1. Demographics and nerve conduction studies across El Escorial degrees of certainty

	Definite (n = 26)	Probable (n = 16)	Possible (n = 10)	Suspected (n = 2)	p value
Age – year	54.1 ± 10.2	52.1 ± 12.3	50.4 ± 14.4	55.5 ± 2.1	0.82
Male gender – n (%)	11 (42.3)	9 (56.2)	6 (60)	1 (50)	0.73
Time from symptom onset to diagnosis – months, median (IQR)	24 (12-61.2)	24 (13-48)	24 (24-72)	60 (24-60)	0.24
Neurophysiologic findings					
Time from symptom onset to neurophysiology study – months, median (IQR	24 (12-45)	24 (12-42)	30 (22.5-72)	55.5 (15-55.5)	0.48
Distal CMAP, median nerve	2.6 ± 2.7	3.6 ± 2.9	4.8 ± 3.1	8.4 ± 2.1	0.025
Distal CMAP cubital nerve	4.0 ± 2.8	5.2 ± 3.0	8.3 ± 3.9	10.9 ± 0.28	0.004
APB/ADM ratio	0.89 ± 0.98	0.61 ± 0.45	0.56 ± 0.24	0.77 ± 0.22	0.54
Split hand phenomenon – n (%)	16 (61.5)	11 (68.7)	8 (80)	1 (50)	0.80

APB: abductor pollicis brevis; ADM: abductor digiti minimi; IQR: interquartile range; CMAP: compound muscle action potential.

Table 2. Split hand ratio and nerve conduction studies across ALS symptomatic stages

	≤12 months (n = 10)	12-24 months (n = 23)	≥24 months (n = 18)	p value
Split hand phenomenon, n (%)	6 (60)	16 (69.5)	13 (72.2)	0.79
APB/ADM ratio	0.61 ± 0.35	0.76 ± 0.51	0.76 ± 1.0	0.80
Distal CMAP, median nerve (mV)	3.2 ± 2.8	4.4 ± 3.5	2.8 ± 2.5	0.23
Distal CMAP, ulnar nerve (mV)	5.6 ± 4.0	5.8 ± 3.9	5.0 ± 4.1	0.75

APB: abductor pollicis brevis; ADM: abductor digiti minimi; ALS: amyotrophic lateral sclerosis, IQR: interquartile range; CMAP: compound muscle action potential.

80% with possible ALS, and in 50% with suspected ALS (Table 1).

Moreover, the split hand phenomenon was identified in 60% of patients within 12 months of symptom onset, 69.5% between 12 and 24 months, and 72.2% after 25 months (Table 2). An example of the split hand sign with further decreased APB/ADM ratio (split hand phenomenon) is shown in figure 1.

Discussion

Epidemiological studies report an ALS male incidence of 3/100,000 inhabitants/year compared to a female incidence of 2.4/100,000 inhabitants/year, with a 1.5:1 ratio. This relationship was not observed in our study since there were 28 men and 26 women, with a 1:1 ratio. About 90% of ALS cases occur sporadically, while 10% are familiar[9,10]. None of our patients had ALS family history. The mean age at diagnosis in our study is 52.8 ± 11.4 years, which is similar to world reports, with only 5% of the patients presenting before the age of 30[10].

Early ALS diagnosis represents a diagnostic challenge when signs and symptoms are not so evident. Therefore, diagnosis at symptom onset is usually delayed in ALS. In our study, we identified that time to diagnosis from symptom onset is 24 months, conversely to what other authors have reported in a range from 8 to 15 months[4]. This might be explained due to a delay in referral time to our center.

ALS diagnosis is defined by El Escorial criteria, which encompasses clinical findings of UMN and LMN. Definite diagnosis includes clinical evidence of UMN and LMN signs in bulbar plus two spinal regions, or three spinal regions[11]. Nonetheless, they do not consider electrophysiologic findings, which may identify earlier

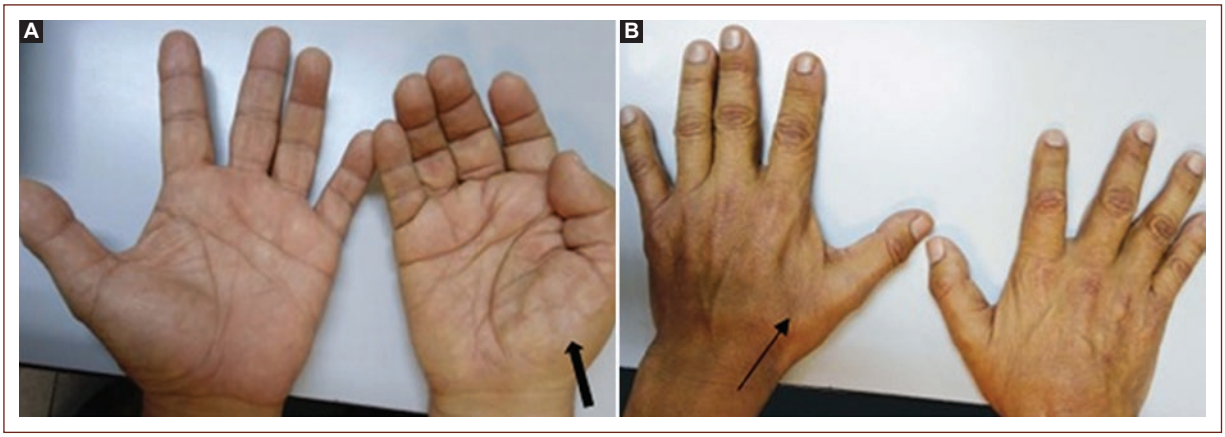

Figure 1. A 65-year-old man with definite ALS diagnosis, who started with the right hand weakness. **A:** Thenar atrophy in the right hand. **B:** First interosseous atrophy of the left hand. CMAP distal APB/ADM ratio was 0.45, consistent with the split hand phenomenon. ALS: amyotrophic lateral sclerosis; CMAP: compound muscle action potential, APB: abductor pollicis brevis; ADM: abductor digiti minimi.

signs of UMN and LMN that are not evident in clinical examination. On the other hand, newer diagnostic criteria such as the Awaji-Jima criteria include both NCS and El Escorial clinical examination, increasing both sensitivity and specificity[12]. Unfortunately, neither El Escorial nor Awaji-Jima considers any early biomarkers. Electrophysiological findings may play an important role in early diagnosis, as some signs may be identified in neurophysiology but not in clinical examination when the disease is in early stages. Other markers as well have been identified as potential early biomarkers such as motor band sign on magnetic resonance imaging (MRI), bright tongue on MRI, pyramidal tract tractography (DTI-MRI), motor evoked potentials by transcranial magnetic stimulation, and cytokine detection in cerebrospinal fluid.

Recently, a group of experts proposed a new definition of ALS in patients with the presence of UMN and LMN dysfunction in at least one body region as well as progressive motor impairment preceded by normal motor function[13]. We consider these as promising criteria for early diagnosis as they consider only UMN and LMN findings in one segment to make the diagnosis, additional to NCS results. Despite no specific curable treatment exists for ALS, early diagnosis has been shown to improve quality of life as multidisciplinary management is promptly implemented[1,2]. Limited information exists regarding UMN dysfunction in electrophysiological studies. Some authors consider F-wave persistence as an indirect marker of UMN compromise. Transcranial magnetic stimulation has been suggested as a marker, however, it requires standardization and is not available in most countries[14].

The split hand phenomenon is defined as decreased APB/ADM CMAP amplitude ratio (< 0.6). This finding implies a greater compromise of thenar compared to hypothenar muscles. Even though both regions are innervated by C8-T1 roots, APB and FDI are muscles with extensive corticospinal connections that are easily affected by glutamate excitotoxicity[6]. Kuwabara et al. reported in a multicenter study that decreased APB/ADM ratio was found in 41% of ALS patients and in 5% of normal controls, which is close related to our findings. They concluded that prominent muscle atrophy in APB and FDI, with relatively preserved ADM, appears to be specific to ALS[7]. In contrast, our overall prevalence of split hand phenomenon in ALS patients was 70%.

Despite controversies on this subject[15], the authors hereby consider the split hand ratio as an UMN finding, commonly found in ALS and extremely rare in healthy subjects[7]. Furthermore, the split hand phenomenon's prevalence appears to be greater in early ALS stages and less prevalent when muscle atrophy increases. About 60% of patients presented the split hand phenomenon within 12 months of symptom onset. No significant differences in prevalence of split hand ratio were observed between early and late ALS. This is an important finding as this may provide a marker for supportive ALS diagnosis in early stages.

Clinicians must be careful as a reduced split hand ratio may be observed in other motor neuronopathies, such as remote polio, monomyelic amyotrophy, or spinal muscular

atrophy, although dissociated small muscle atrophy is most frequently seen in ALS[6]. Limitations of the present study include the small number of patients and the retrospective character. Other limitation was that data collection was performed during routine clinical practice.

Conclusion

The split hand phenomenon is commonly found across all different degrees of certainty of El Escorial clinical diagnostic criteria. Similarly, it is also commonly encountered in the early stages of the disease. We provide evidence for a neurophysiological tool in the aid of early diagnosis of ALS. This should serve as background for further studies to identify early neurophysiologic markers in this disease. Our findings could improve diagnostic yield in the forthcoming studies and provide clinical and paraclinical biomarkers in this incurable disease.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Drug-induced parkinsonism: what should a psychiatrist know?

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Abstract

Drug-induced parkinsonism is the main cause of secondary parkinsonism in the world. Antipsychotics, antidepressants, and mood stabilizers are the most common drugs implicated in the parkinsonism. This is why psychiatrists and neurologists must have deep knowledge of the diverse aspects of these disorders, to take the best diagnostic and therapeutic approaches.

Key words: *Parkinsonism. Drug-induced parkinsonism. Psychiatrist.*

Parkinsonismo inducido por medicamentos: ¿Qué debería conocer el psiquiatra?

Resumen

El parkinsonismo inducido por medicamentos es la principal causa de parkinsonismo secundario en el mundo. Los antipsicóticos, antidepresivos y moduladores del estado de ánimo son los medicamentos más frecuentemente implicados en el desarrollo de este trastorno. Por tanto, es necesario que psiquiatras y neurólogos conozcan profundamente las diversas características del parkinsonismo inducido por medicamentos, para tomar las mejores decisiones diagnósticas y terapéuticas en estos pacientes.

Palabras clave: *Parkinsonismo. Parkinsonismo inducido por medicamentos. Psiquiatría.*

Introduction

Drug-induced parkinsonism (DIP) is a clinical syndrome characterized by bradykinesia, tremor, stiffness, and postural instability. Idiopathic Parkinson's disease (PD) and DIP represent the two main causes of parkinsonism in the world[1]. In the 50s, the first DIP descriptions were made, and they linked the syndrome to the use of chlorpromazine and reserpine, drugs that were used at the time as antipsychotic and antihypertensive, respectively[2]. In later years, parkinsonism was recognized as a frequent adverse effect related to different antipsychotic drugs and later to other numerous drugs of other pharmacologic groups (Table 1).

Objective

The purpose of this article is to contribute to a bigger understanding and recognition of DIP through an updated description about clinical and therapeutic aspects, etiology, and physiopathology, diving into key concepts and situations for the psychiatrist.

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Table 1. Drugs associated with DIP

Mechanism	Pharmacological group/drug
D2 receptors blockers (typical and atypical)	Typical antipsychotics: haloperidol, levomepromazine, etc. Atypical antipsychotics: risperidone, olanzapine, ziprasidone, aripiprazole, quetiapine
Depletion of dopamine	Tetrabenazine
Dopamine synthesis blockers	Alpha methyldopa
Calcium channels blockers	Flunarizine, cinnarizine
Antiemetics	Metoclopramide
Calcium channels blockers	Diltiazem, verapamil
Antiepileptics	Valproic acid, phenytoin, levetiracetam
Mood stabilizers	Valproic acid, lithium
Antiarrhythmics	Amiodarone, procaine
Immunosuppressors	Cyclosporine, tacrolimus
Antidepressants	Fluoxetine, sertraline
Antivirals	Acyclovir, vidarabine, antiretrovirals

Methodology

A literature research in the PubMed database was made, using a combination of the following key words: "DIP," "parkinsonism AND neuroleptics," "parkinsonism AND antidepressants," "parkinsonism AND mood stabilizers," "parkinsonism and psychiatry," and "parkinsonism and drugs." Additional articles used as references from the obtained articles of the mentioned research were also included. We selected publications in English and Spanish. We reviewed the articles and chose the ones that enabled to reach the aim of the present study.

Epidemiology

Savica et al. found 11,9% of parkinsonism in the Olmstead county, Minnesota, between 1976 and 2005, corresponded to DIP and the estimated incidence rate was 3,3/100,000 persons-year[1]. Furthermore, they identify a tendency toward a decrease in the rate of DIP incidence of the 68,6% from 1976 to 2005[1]. In Korean population, the reported incidence has been greater than the one described in American population and in contrast to America, the Korean records showed an increase of DIP incidence from 7,1 to 13,9/100,000 persons-year in 2012 and 2015, respectively ($p < 0,0001$)[3].

Among Latin-American population, some studies evaluated the epidemiology behavior of DIP. The Pietà study made in Brazil found that DIP represents the 12,3% of parkinsonism cases with a raw prevalence of 1300 cases/100,000 people[4]. This estimate was lower compared to the one reported in the previous studies in Brazilian population as well[5]. In specific scenarios, such as neurology and movement disorders consult, studies report that between 6,8% and 56% of evaluated patients for parkinsonism correspond to DIP[6,7]. Despite the described studies, the incidence and prevalence of DIP remains unknown due to a lack of record of this syndrome and the frequent confusion between DIP and idiopathic PD[7,8].

Risk factors

The OMS pharmacovigilance database analysis (Vigibase®) showed that people over 75 years old are at the highest risk of developing this disorder (reporting odds ratio [ROR] = 2,12; IC 95% 1,98-2,26)[9]. Some factors may explain the risk in this population, such as higher exposure to drugs for behavior disorders, higher polypharmacy, higher risk for cognitive impairment, and less nigrostriatal integrity[10,11].

Many studies have reported a higher DIP frequency among women[11]. However, Germany et al. found the risk for DIP was higher in men compared to women (ROR = 1,39, IC 95%: 1,31-1,47)[9], when they adjusted the total ratio of pharmacological adverse effects reports. Furthermore, genetic factors have been associated with higher predisposition to parkinsonism development, therefore not everyone exposed to antipsychotics develop this disorder[10,12].

Key elements for definition

DIP is defined as a parkinsonian syndrome secondary to the use of drugs, which alters the dopaminergic function in persons without previous parkinsonism history[1]. A key aspect when drugs are linked with parkinsonism development is the existence of a temporal relationship between the use of a drug to the emergence of symptoms[13]. However, the gap between the initiation of a drug and the parkinsonism manifestation is variable, going from a few days to months[14,15]. The French pharmacovigilance database analysis enabled to identify two peaks in the emergence of symptoms. The initial peak occurred in the first 3 months of drug

use and it was mainly associated to D2 receptor blockers and antidepressants. The second peak occurred between 9 and 12 months and it was especially associated to calcium channel blockers[14,15]. On the other hand, it is considered that the parkinsonian syndrome resolution must come in the first 6 months after the drug suspension, although this time is also variable and controversial[15-17].

Physiopathology

Movement control involves many cortical and subcortical regions. The planning and movement performance starts in the premotor and motor areas of the cerebral cortex; while the basal nuclei, the substantia nigra, the subthalamic nucleus, and the red nucleus among others also play a fundamental role in the reception, integration, and regulation of the information coming from the cerebral cortex, cerebellum, and other nervous system regions[18]. A great number of neurotransmitters interact in these cerebral regions, including monoamines, acetylcholine, glutamate, and gamma-aminobutyric acid (GABA)[18].

The main central dopaminergic pathways are the nigrostriatal, mesolimbic, and mesocortical, which emerge from the substantia nigra, the ventral tegmental area, and the retrorubral region[19]. The substantia nigra regulates the basal ganglia and its effect is mediated by dopamine. Until now, five types of dopamine receptors have been described, from D1 to D5, grouped in two families, D1-like and D2-like[20]. The D1-like family includes D1 and D5 and they are characterized by Gs protein coupled receptors, they stimulate adenylyl and increase the intracellular cAMP levels, in general, they lead to an excitatory effect. The D2-like family includes D2-D4 receptors, they are Gi protein coupled receptors and their stimulation induces opposite effects to the ones described for the D1-like receptors family[18,20].

The antipsychotics block the D2 receptors in the mesolimbic and mesocortical pathways. In the corpus striatum, the D2 receptor stimulation, the inhibitory kind, regulates the GABA release in the striatal neurons, avoiding the excess of an inhibitory tone in the indirect pathway and maintaining a balance with the direct pathway[21]. Drugs that alter the nigrostriatal pathway may modify the dopamine mediated negative feedback toward the corpus striatum, which induce a deeper activation and an increase of the inhibitory tone coming from the striatum[19]. It has been estimated that the emergence of parkinsonian symptoms comes when more than 80% of the D2 receptors are blocked[22]. However, not only the percentage of occupied receptors is important but also the drug-receptor union. Drugs like aripiprazole may reach more than 90% of blockage without producing parkinsonian symptoms, it seems to be explained by a high drug-receptor clearance rate[23].

The hyperkinetic symptoms observed in DIP, such as oromandibular dyskinesia, may be also explained by the prolonged blockage of dopaminergic receptors; but in this case, the dyskinesia is due to the compensatory hypersensitivity they develop[24]. Other implicated mechanisms include type 2 vesicular monoamine transporter 2 blockage and the modification of calcium channels at the presynaptic terminal[25].

Drugs associated with parkinsonism

Numerous drugs from different pharmacological groups frequently used in the neurology and psychiatric practice have been associated to parkinsonism emergence.

Antipsychotics

Up to 60% of DIP cases have been attributed to the psychopharmaceutic drugs, especially antipsychotics[26]. In general, a higher risk is attributed to typical antipsychotics because these drugs have a greater affinity and minor speed of clearance over the D2 receptors, while the atypical antipsychotics may have a more restricted effect over the 2A serotonin receptors[27]. However, the risk of parkinsonism with atypical antipsychotics is variable and, in general, when high dosage is used, their risk is comparable to the risk of typical antipsychotics[28]. Gomez et al. evaluated this risk among patients with schizophrenia, who frequently get high dosage of this drugs and they found that the DIP prevalence was similar among patients, who got both types of antipsychotics[29].

Risperidone, an atypical antipsychotic, has a dosage-dependent action on D2 receptors, therefore, their effect at a high dosage emulates a typical antipsychotic action[27]. Olanzapine is another atypical antipsychotic that has shown a high potential to induce parkinsonism and other extrapyramidal effects[27]. On the other hand, aripiprazole is an atypical antipsychotic, with a novel mechanism of action and a fast speed of clearance from the receptor. Initially, there was considering that aripiprazole had a low risk of inducing parkinsonism, although this has been controversial in recent publications[23]. The two antipsychotics with the lowest risk for parkinsonism are clozapine and quetiapine[27,30].

Antidepressants

Although rare, the association between antidepressants and parkinsonism has also been reported. A retrospective study of pharmacovigilance reported that 8% of DIP cases have been associated with the use of antidepressants[15]. Among these drugs, serotonin reuptake inhibitors and dual-action antidepressants stand out, especially sertraline and escitalopram[15]. Hawthorne et al. found that parkinsonism was the most frequent extrapyramidal reaction associated with antidepressants and 80,2% of all the extrapyramidal effects were associated with serotonin reuptake inhibitors[31]. It is believed that the mechanism by which the antidepressants may induce parkinsonism is because of the increase of the serotoninergic activity at the raphe nucleus, which generates an inhibitory action over the striatal and tegmental dopaminergic pathways[31].

Mood stabilizers

Mood stabilizers may also induce extrapyramidal effects[32]. Among this group, the valproic acid is the drug which associates the most with tremor and parkinsonism[32-34]. This drug has several mechanisms of action, the blockage of voltage-dependent sodium channels and the inhibition of GABA-metabolizing enzymes generate an increase of GABA in the striatum nuclei, this mechanism may explain its parkinsonian effects[33,34]. Strikingly, it has been described that there is no direct relationship between serum valproic acid levels and the development of parkinsonism; furthermore, the emergence of symptoms may appear even years after the start of the drug[33,34]. Zadikoff et al. reported parkinsonism in 10% of patients taking valproic acid[32].

Persistent DIP: DIP or idiopathic PD?

Up to 30% of the patients with DIP may present a persistent or progressive parkinsonian syndrome[35]. The persistence or the deterioration of parkinsonian syndrome, as well as a complete remission with posterior symptom recurrence after the suspension of the drug, may indicate the existence of a preclinical idiopathic PD state, which was uncovered by the drugs[35]. In fact, it has been reported that just 43% of patients with DIP presented normal activity in the nigrostriatal system, which may indicate that a great amount of DIP patients really corresponded to PD uncovered by drugs more than a pure DIP[36,37].

Although clinical manifestations alone are not sufficient to differentiate PD and DIP, some authors have reported semiologic differences that may orient the differentiation[35]. The presentation of idiopathic PD is slow and progressive, while DIP has usually a subacute start and the evolutions tend to be stationary[38]. In addition, Yomtoob et al. reported that patients with more than main two manifestations of parkinsonism have a greater probability of having PD than DIP[26]. Several studies have described a greater asymmetric parkinsonian prevalence among PD uncovered by drugs than a pure DIP[36,39]. Pieters et al. found 20,8% of DIP patients presents with asymmetric parkinsonian symptoms and the asymmetric presentation was associated with a greater severity of symptoms, especially cognitive behavioral symptoms and psychopathology[40]. However, even one-third of pure DIP patients may also exhibit asymmetric parkinsonian symptoms[39]. Other more frequent characteristics of DIP are hypomimia, akinetic-rigid phenotype, upper extremities impairment, and higher frequency of postural tremor[41].

Non-motor symptoms may also be crucial for the differentiation of these two types of parkinsonism. Morley et al. found that non-motor symptoms such as constipation ($p = 0,02$) and erectile dysfunction ($p = 0,05$) were significantly more frequent in PD than in DIP. On the other hand, cognitive complains and psychopathology were higher in DIP. Although hyposmia was frequent in DIP and PD (88% vs. 57%), it was significantly more frequent in DIP ($p = 0,003$)[41]. The evaluation of the olfactory function is a tool with a good performance for this differentiation and the result of the olfactory test may predict with great accuracy if patients with parkinsonism could recover after the suspension of the involved drug[41,42]. Kim et al. evaluated other symptoms using the non-motor symptoms scale in patients with PD, DIP, and healthy controls, they found that symptoms such as urinary and sleep impairment, attention deficit, and hyposmia were associated with PD, even after adjusting confounding variables[43].

Treatment

The management of DIP includes prevention, early recognition, and modification of the pharmacological therapy that is potentially causing parkinsonism[7]. Because DIP is an iatrogenic manifestation, doctors must be aware of the safety profile of the drugs they prescribe and the characteristics of the patients, especially older patients. Patients with high risk for developing

DIP receiving drugs that alter dopaminergic function must be evaluated regularly with the intention to detect early parkinsonian symptoms[44].

The main DIP treatment is the suspension of the involved drug. In some cases, there is no need to change the drug for another. For example, some patients with migraine treated with valproic acid or flunarizine, who have achieved good symptoms control, do not need to continue the drug nor change it. However, in other cases, a change of the drug is needed, such as patients receiving typical antipsychotics, who may benefit from a change to an atypical antipsychotic. Patients using an atypical antipsychotic such as risperidone may improve with a change to another atypical antipsychotics with lower parkinsonism risk such as clozapine or quetiapine. Patients cannot change the implicated drug because of their illness, the drug must be reduced to the minimum possible dosage[44].

Amantadine and anticholinergics, including biperiden, benztropine, or trihexyphenidyl, have been used for the control of symptoms but they lack strong evidence to support their use[25,44].

Prognosis

The majority of DIP cases are reversible with the suspension of the drug, that is, why DIP prognosis is usually benign. However, up to 30% of patients with DIP may develop a persistent or progressive parkinsonian syndrome and there is the hypothesis that many of these patients have another cause of parkinsonism. Yoo et al. reported that patients, who reach a full recovery, showed greater functional connectivity in prefrontal and cerebellar regions[45]. On the other hand, there is a possibility that DIP behaves as a risk factor for PD. For example, a cohort study showed that the long-term risk for PD increased 2,3 times after the exposure to neuroleptics[46].

It seems that the complete remission of parkinsonian symptoms after the suspension of the drug is not an accurate indicator of DIP diagnosis. A study of autopsies found pathological findings matching PD in two patients who have had DIP diagnosis and have reached a complete remission of symptoms after the drug suspension[47].

Functional imaging has shown a good performance predicting the evolution of parkinsonism with great diagnostic utility. However, patients with DIP and normal activity of the dopamine transporter may also present persistence of parkinsonism[48].

Conclusion

DIP is one of the main causes of parkinsonism in the world and this syndrome will continue to be an important cause of morbidity, especially in older population. In most cases, DIP is a pure syndrome without dysfunction of the nigrostriatal system. However, a variable but significant percentage of patients presents previous disturbances in the nigrostriatal system, which allows to think that in these cases the drug uncovers a previous neurodegenerative disease. In both cases, parkinsonism has an important morbidity for patients, therefore, it is important to prevent it and to recognize it in early stages to limit its clinical impact.

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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REVIEW ARTICLE

Do we need to redefine the advanced stage in Parkinson's disease?

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Abstract

Identifying the advanced stage in Parkinson's disease (PD) is crucial for shifting from conventional to device-aided therapies. The criteria to define the onset of advanced PD have been based on lengthy and disabling daily off-times, troublesome dyskinesia and complex therapeutic regimes, but have also included invalidating non-dopaminergic symptoms, such as dementia, falls or dysphagia. These last problems usually appear in a much later stage of the advanced PD. The key to the definition of advanced PD should be the lack of adequate PD control of both motor and non-motor dopaminergic symptoms. The patient's judgment about the quality of their response to conventional therapy is also critical to establish the advanced stage. The early identification of this phase allows maintaining the patient's functional state whenever appropriate treatments are applied. We should keep the term advanced stage when the dopaminergic symptoms responsive to device-aided therapy are preponderant. When invalidating non-dopaminergic symptoms dominate the clinical picture, the term post-advanced stage could be more suitable.

Key words: *Parkinson's disease. Advanced stage. Post-advanced stage. Dopaminergic symptoms. Non-dopaminergic symptoms.*

¿Necesitamos redefinir el estado avanzado en la enfermedad de Parkinson?

Resumen

La identificación del estadio avanzado en la enfermedad de Parkinson (EP) es crucial para el cambio del tratamiento convencional al de segunda línea. Los criterios para definir el inicio de la EP avanzada se han basado en períodos off largos e invalidantes, discinesias molestas y regímenes terapéuticos complejos, pero también se han incluido síntomas no dopaminérgicos graves, como demencia, caídas o disfagia. Estos últimos problemas habitualmente ocurren en un estado de la EP avanzada más tardío. La clave para la definición de EP avanzada está en la falta de control adecuado tanto de síntomas motores como no motores. La opinión del paciente sobre la respuesta o su falta al tratamiento convencional debería ser clave para la definición del estadio avanzado. Su identificación temprana permite mantener la calidad de vida del paciente, siempre que se aplique el tratamiento apropiado. Deberíamos utilizar el término enfermedad avanzada para la fase en que dominan los síntomas dopaminérgicos que responden a los tratamientos de segunda línea. Cuando los síntomas no dopaminérgicos invalidantes dominan el cuadro clínico, el término estadio sobrepasado parece más adecuado.

Palabras clave: *Enfermedad de Parkinson. Estadio avanzado. Estadio sobrepasado. Síntomas dopaminérgicos. Síntomas no dopaminérgicos.*

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Introduction

Parkinson's disease (PD) is a chronic process that may affect the patient for many years and goes through various stages[1]. Most authors divide the disease's natural history into a premotor or prodromal stage, an early stage, an intermediate stage, and an advanced stage. During the early stage, dopaminergic drugs at low doses provide good control for the whole day. In the intermediate stage, frequent drug adjustments are needed to control the symptoms. The advanced stage occurs when conventional therapy (see below) does not provide the patient with an adequate disease control[2].

Although the term advanced PD has been widely used, it is still not very well-defined[3]. Identifying it clearly is a key issue since we have specific treatments for this stage.

In this review, we try to analyze the advanced PD fundamentals. First of all, we divide the parkinsonian symptoms according to their response to dopaminergic medication, the only available. Both conventional and device-aided treatments only act on dopaminergic symptoms. The failure of the first group marks the onset of advanced PD. This should lead to a switch to device-aided therapies. Unfortunately, this is not always the case. Not infrequently, patients are referred to surgery or infusion therapies after years with poor control on conventional therapy. We describe the works of different groups searching for criteria to identify patients with advanced PD and their limitations, in our opinion. Finally, we propose some keys to improve the identification of this stage. We consider it critical the decline of the functional impact in daily activities with conventional treatment, no matter whether the symptoms are motor, non-motor or both. The patient's judgment about this decline is essential to establish the advanced stage. This judgment does not always match with the rating scales used by the neurologist. We also think that the presence of invalidating non-dopaminergic symptoms, such as dementia, on-freezing gait or orthostatic hypotension, should define a stage different from the advanced.

Relevant issues in advanced PD. Treatments and symptomatic response

PD is, in fact, a multiple system degenerative condition. Apart from the substantia negra pars compacta, there is neuronal loss in areas such as the olfactory system, autonomic nerves, peduncle pontine nuclei, locus coeruleus, and raphe nuclei *nucleus basalis* of Meynert, limbic system or the associative cortex[4]. This broad degeneration explains many PD symptoms different from tremor, ridigity, and bradykinesia, the classic triad. Any therapy currently available only acts on the pathways modulated by dopamine, either binding the dopaminergic receptor or modifying the subthalamic nucleus hyperactivity, as in the case of surgery.

Over the last years, much attention has been paid to PD's non-motor symptoms[5,6]. Nevertheless, from a practical point of view, it could be more useful to divide PD symptoms into dopaminergic and non-dopaminergic. The first group responds to dopaminergic drugs, while the second group does not. The Sydney study followed up a cohort of PD patients for 15 years. After this time, non-dopaminergic symptoms become much more disabling than dopaminergic ones for most patients[7].

It is very important to learn which symptoms respond to dopaminergic medication. In this way, the neurologist may design the best possible therapeutic strategy, and the patient knows what to expect from the treatment.

In table 1, we have divided the Parkinsonian symptoms into dopaminergic and non-dopaminergic. The most troublesome non-dopaminergic symptoms are on-freezing gait, autonomic disorders, particularly orthostatic hypotension, and cognitive decline, which progresses to dementia in 80% of the cases[7,8].

Invalidating non-dopaminergic symptoms occur in later stages of PD and dramatically constrain the patient's daily activities. Before reaching this step, our current therapeutic capacity, properly applied, may extend the patient's functionality for a long period, even when the oral dopaminergic medication starts to fail.

Nowadays, the available PD therapy can be divided into two groups, conventional[2] and device-aided treatment[9]. The first group includes oral drugs and the rotigotine patch. The second one is formed by deep brain stimulation (DBS), continuous apomorphine infusion (APO), and intrajejunal levodopa (DUO).

When only conventional treatment was available, the patient got into a very disabling situation once it failed. The term advanced PD was coined to describe this situation, meaning a terrible and progressive life quality loss until death.

With the advent of device-aided therapies, the picture has completely changed. Several studies[10-12] have shown that either DBS or infusion treatments allow for reasonable control of PD symptoms for many years.

Table 1. Dopaminergic and non-dopaminergic symptoms in Parkinson's disease

Dopaminergic symptoms		Non-dopaminergic symptoms	
Motor	**Non-motor**	**Motor**	**Non -motor**
Bradykinesia	Pain*	On-state freezing	Dementia
Rigidity	Depression*	On-state balance disturbance	Psychosis
	Apathy*		
Tremor	Anxiety *	On-state dysphagia	Autonomic disfunction
	Urinary urgency*		
	Lack of concentration		

*These symptoms may also have a non-dopaminergic origin and, therefore, fail to respond to dopaminergic drugs.

Since these device-aided therapies have been available, a reliable way to identify the advanced PD stage's onset has become crucial. The neurologist must be aware when the disease control starts to decline with conventional therapy and change to device-aided therapies. Hence, a definition for advanced PD should not be academic but operational, as it should give rise to a shift of therapeutic paradigm.

Another important issue is whether to call advanced stage to the whole period when conventional therapy is not sufficient for a good PD control. The patient's management is quite different when dopaminergic symptoms are dominant or when invalidating non-dopaminergic symptoms play the clinical picture's central role.

Due to the negative connotations the term advanced evokes, some authors have proposed different names, for instance, complex stage[3].

The search for criteria of advanced PD

The availability of device-aided therapies has prompted the search for operative criteria to define advanced PD. Some pitfalls complicate this search, such as the absence of biomarkers, the disease heterogeneity, the patient's personal experience with the disease, the patient's employment status or the presence of non-dopaminergic symptoms, sometimes overlooked.

The NAVIGATE-PD study[13] interviewed 103 experts from 13 countries about operative criteria to consider device-aided therapies, DBS, APO, and DUO. They concluded that loss in quality of life was the critical point. They proposed that (1) taking levodopa 5 or more times per day, (2) daily troublesome off-time over 1 or 2 h, or (3) severe dyskinesia, with no specific duration, were red flags for possible advanced PD.

A group of Spanish neurologists carried on the CEPA (*Consensus about the definition of advanced PD*), also called CDEPA (*Questionnaire for advanced PD*), study[14,15]. They administered a questionnaire to other 240 Spanish neurologists, with a preferential dedication to PD, about possible advanced stage criteria, applying the Delphi method. The panellists considered as definitive symptoms (1) the need for aid in the daily activities, (2) severe motor fluctuations, (3) severe dysphagia, (4) falls, and (5) dementia. The critical factor to the advanced stage was the disease duration.

Another study, with the Delphi method, involved experts from ten European countries[16]. The goals were to define clinical indicators for advanced PD, criteria for device-aided therapies, and the patients more suitable for each one of them. The panellists regarded the following clinical characteristics as suggestive of advanced PD. They are divided into three categories and ranked by order of importance.

1. Motor symptoms: moderate level of troublesome motor fluctuations, at least 2 h of the waking day with off-symptoms, at least 1 h of the day with troublesome dyskinesia, moderate level of dyskinesia, troublesome dysphagia, and daily oral levodopa at least 5 times a day
2. Non-motor symptoms: mild level of dementia, non-transitory troublesome hallucinations, moderate level of psychosis, non-motor fluctuations, and moderate level of nighttime sleep disturbances
3. Functional impact: repeated falls despite optimal treatment, need for help with the activities of daily life at least some of the time, inability to perform complex tasks at least some of the time, and moderate impaired mobility.

In the case of patients with advanced PD candidates for device-aided therapies, the clinical characteristics were reduced to:

1. Motor symptoms: troublesome dyskinesia and off-periods, at least 2 h of off-time, off-period postural instability, dystonia with pain, and freezing of gait during off
2. Non-motor symptoms: nighttime sleep disturbances, with no other specification

3. Functional impact: limited activities of daily life.

The OBSERVE-PD study[17] tried to correlate these clinical indicators with the neurologist's global assessment for advanced PD. It included 2615 patients from 18 countries. The correlation obtained was moderate (K=0.430; 95% IC 0.406-0.473). According to their neurologists, within the patients diagnosed with advanced PD, 66% met the criteria for device-aided therapies. The authors highlighted that not all the patients treated with these therapies had advanced PD. As no more information was available, the authors speculate about the possible indications, such as poor levodopa tolerability, refractory non-motor symptoms, uncontrollable tremor, or functional needs in younger patients. Curiously, they did not consider these three latter situations as advanced PD.

The recent MANAGE-PD study has attempted to rank the criteria to identify advanced PD[18]. The authors split the patients into three categories. Category 1 encompasses patients adequately controlled on conventional therapy. In Category 2, conventional therapy must be optimized to improve PD control. Finally, in Category 3, the disease control with this medication is not adequate, despite the optimization. To screen the patients, they applied two filters. The first one consists of checking whether the patients have at least one of these criteria: (1) 5 or more daily levodopa doses, (2) daily off-time of at least 2 h, (3) unpredictable motor fluctuations, (4) troublesome dyskinesia, and (5) limitation in at least one activity of daily life. Meeting one or more of these problems should lead to a second filter to determine whether the patients need optimization or device-aided therapy. To validate these criteria, the authors presented ten clinical pictures with the three categories to 20 neurologists.

The importance of the patient's judgment for the early identification of the advanced stage

The aim for the early identification of advanced PD and the consequent shift in the therapeutic paradigm is to maintain the best possible patient's functionality. To achieve this, the neurologist must apply the appropriate therapy for each stage. The critical point is the change from intermediate to advanced PD since this should mean different disease management.

The recent study *Euroinf 2* presents the characteristics of a cohort of 173 patients treated with device-aided therapies. It results quite striking that many patients start with some of these therapies in very advanced stages or even with remarkable axial symptoms[19]. Sometimes patients are on conventional therapy when they should have been on a device-aided therapy long before. For this reason, it is essential to identify when conventional therapy optimization is no longer the best option.

Most authors agree that the advanced stage commences when conventional treatment optimization does not provide *adequate control* for the disease[2,14,15,18]. The term *adequate control* may be too vague as it depends on the neurologist's judgment and, mainly, on the patient's perception, demands, and expectations. Although there are some general recommendations, both conventional and device-aided PD therapies should always be personalized. The division of PD into different stages is not an abstraction. It must be adapted to each patient's reality, being, therefore, an operational definition.

The need for personalizing each case is well underlined in the aforementioned OBSERVE-PD study[17]. The correlation between the patient's neurologist's judgment and the criteria from a group of experts is only moderate. In the validation of the CEPA study[15], the authors remark that the neurologist clinical judgment is the gold standard to determine the PD stage.

A point regarded as key in some study is the PD duration[14]. However, this condition is not always related to the disease stage. In our personal experience, the average disease duration before the onset of device-aided treatments has been eight and a ½ years. Out of them, 30% were on these therapies after 6 years of PD (personal data not published). At the opposite end, there are patients with PD for over 20 years with sufficient autonomy had no dementia[20,21]. Although after 5 years, half of the patients get motor fluctuations[22], a minority remains in good condition with no need for drug adjustments or significant non-motor symptoms after over 10 years[23]. Hence, we think that the PD duration is not a reliable indicator of the advanced stage.

As mentioned above, the MANAGE-PD study[18] considers three red flags for possible advanced PD, daily off-state over 2 h, troublesome dyskinesia and 5 or more daily levodopa doses. Many levodopa doses mean several adjustments, but patients may have a reasonable control on 5 daily levodopa dose. If these adjustments do not avoid troublesome dyskinesia, the patient has bad PD control and advanced PD. The issue of the off-state is not so straight. Although a daily 2-h off-state is a red flag in PD, we must consider as well how the patient experiences this problem and how

it affects their functional situation. Patients with demanding jobs may feel significantly limiting an off-state of 1 h a day. In contrast, more aged patients with no job responsibilities may tolerate better off-periods even over 2 hours. Hence, the patient's judgment may be more valuable than a score on a rating scale when both do not match.

Besides, we have to take into account the off-period duration and intensity, and not only motor but also non-motor symptoms. Pain, anxiety, apathy, depression, or lack of concentration may be very disabling during the off-state with or without motor symptoms. At our site, we have seen patients with episodes of severe off-state pain lasting < 1 h, only responsive to infusion treatments. We also think that we should include within the advanced stage cases with disabling tremor, even if the other Parkinsonian symptoms do appropriately respond to conventional medication. Finally, we must not forget the patients with faltering on-state, even without important fluctuations. As this is mainly due to gastroparesis, a treatment skipping the oral route is usually effective.

A stage beyond the advanced stage

Nowadays, the advanced PD stage encompasses the whole period from the onset of the conventional treatment failure to the disabling non-dopaminergic symptoms dominance. However, this is not a homogeneous period with similar management. Many patients with device-aided treatments carry on an independent life. This does not happen with disabling non-dopaminergic symptoms.

Some studies searching for advanced PD criteria give the same defining value for advanced PD to dopaminergic symptoms refractory to conventional treatment and disabling non-dopaminergic symptoms. Both the CEPA study[14,15] and the 2018 consensus study[16] include as advanced PD criteria dementia, falls or on-state dysphagia, non-responsive to dopaminergic medication, along with dopaminergic symptoms, such as off-time pain, depression, and dyskinesia, all of them responsive to device-aided therapies. The patient's functionality is different enough to consider these situations as two distinct stages of PD.

The presence of disabling non-dopaminergic symptoms is not a contraindication for device-aided therapies but diminish their efficiency dramatically. Only infusion treatments, with low doses and close follow-up, are to try.

Table 2. Keys for the advanced Parkinson's disease

Conventional therapy does not provide *adequate* Parkinson's disease *control*
The term *adequate control* encompasses both motor and non-motor symptoms
The term *adequate control* must be personalized. It is very important the patient's perception of the treatment's functional impact
The identification of this stage should involve a shift to device-aided therapy
The earlier we identify this stage, the earlier we will be able to improve the patient's quality of life
Device-aided therapy only alleviates dopaminergic symptoms, either motor or non-motor
The term advanced Parkinson's disease should be restricted to the situation in which dopaminergic symptoms do not respond to conventional drugs, and non-dopaminergic symptoms are not disabling
If non-dopaminergic symptoms are disabling, we should speak of post-advanced stage

We suggest keeping the name *advanced stage* for the situation in which dopaminergic symptoms dominate the clinical picture but do not respond sufficiently to conventional treatment. Conversely, we consider a new PD stage for the situation in which disabling non-dopaminergic symptoms are dominant. In this case, the patient's functional state is severely diminished, and the therapeutic options significantly reduced. We propose calling this phase *post-advanced stage*. Something in this respect has been previously suggested[15]. In this study, the authors divide the advanced stage into advanced and late. Their criteria are the response to conventional therapy, partial in the first case, absent in the second. They do not mention refractory non-dopaminergic symptoms.

Table 2 shows the keys to advanced PD.

Conclusions

The key to advanced PD's definition stems from the lack of disease adequate control on conventional therapy. The early identification of this phase allows switching to device-aided therapies, which alleviate dopaminergic symptoms, either motor or non-motor. To determine advanced PD, a key point is the worsening of the patient's functional state. We must consider the off-period duration and its intensity, faltering on without fluctuations or disabling non-motor symptoms. The patient's judgment about their situation is essential to assess this stage. Sometimes it does not match with the rating scales.

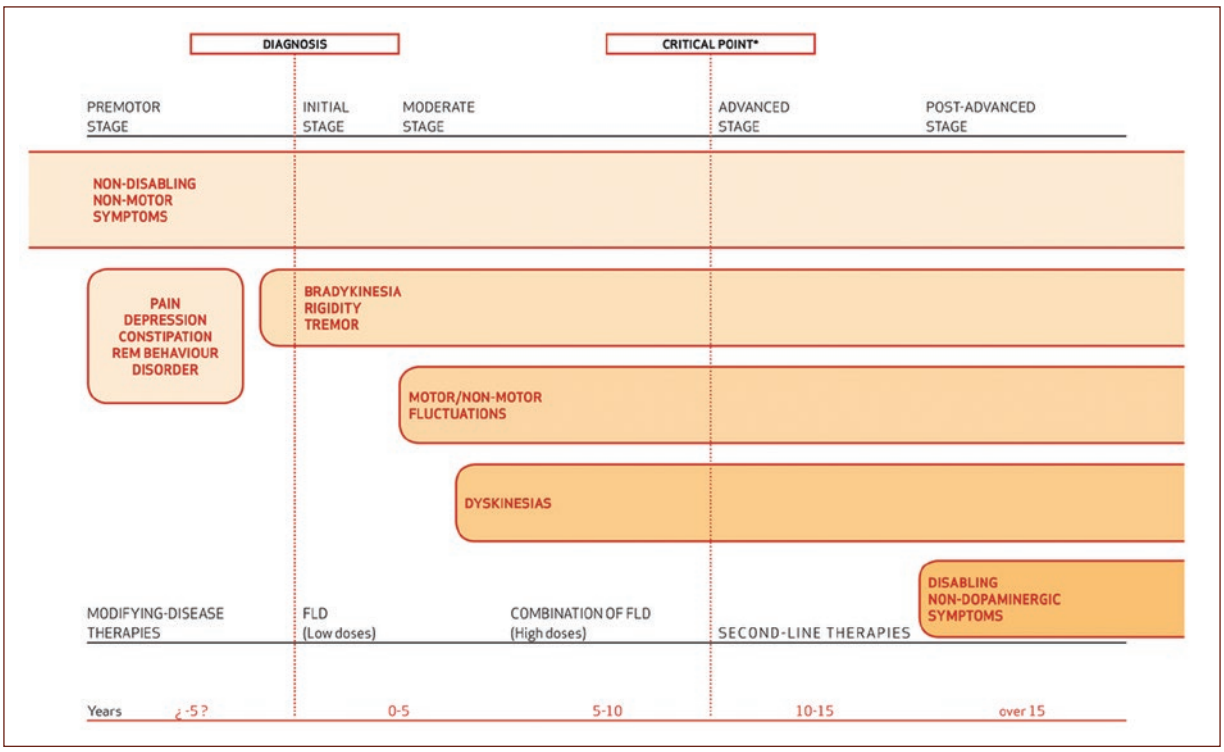

Figure 1. The natural history of PD. FLD first-line drugs (conventional therapy). *Critical point: the situation in which FLD became ineffective.

The patient's functionality in the advanced stage will depend on the presence of disabling non-dopaminergic symptoms. These symptoms usually appear in a later phase. We propose, therefore, differentiating two situations within what is called now advanced state. We should restrict this name advanced stage to the phase in which dopaminergic symptoms are dominant and respond to device-aided therapies. If disabling non-dopaminergic symptoms are present, we should speak of post-advanced stage.

Figure 1 shows a picture of the EP natural history, including the post-advanced stage.

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Conflicts of Interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Obstructive sleep apnea (OSA) should be considered a comorbidity as a risk factor for COVID-19 fatality: A review. Part II

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Abstract

The COVID-19 outbreak caused by the SARS-CoV-2 virus turned into a pandemic and from the first reported cases in December 2019-December 31, 2020, more than 82 million positive cases have been reported with a cumulative fatality of 1,806,155 people due to the complication of a mild upper respiratory infection to a severe lower respiratory disease, such as acute respiratory distress syndrome, and death from multiple organ failure. Comorbidities such as obstructive sleep apnea (OSA) that have a high prevalence in older adults with obesity, should be considered as an additional risk factor for fatality, due to endothelial dysfunction secondary to hypoxia coupled with an increase in the inflammatory cascade with dysfunction of the glymphatic system during sleep in response to SARS-CoV-2.

Key words: *OSA. COVID-19. Comorbidities. Risk factors.*

La apnea obstructiva del sueño (AOS) debería ser considerada una comorbilidad como factor de riesgo para la letalidad de COVID-19: revisión. Parte II

Resumen

El brote de COVID-19 causado por el virus SARS-CoV-2 se convirtió en una pandemia y desde los primeros casos registrados en diciembre de 2019 hasta el 31 de diciembre de 2020, se han reportado más de 82 millones de casos positivos con una fatalidad acumulada de 1,806,155 personas debido a la complicación de una infección leve de las vías respiratorias superiores a una enfermedad grave de las vías respiratorias inferiores, como el síndrome de dificultad respiratoria aguda, y muerte por insuficiencia orgánica múltiple. Comorbilidades como la apnea obstructiva del sueño (AOS) que tienen una alta prevalencia en adultos mayores con obesidad, es un factor más de riesgo de letalidad, por la disfunción endotelial secundaria a la hipoxia aunada al incremento de la cascada inflamatoria con disfunción del sistema glinfático durante el sueño en respuesta al SARS-CoV-2.

Palabras clave: *COVID-19. AOS. Comorbilidades. Factores de riesgo.*

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COVID-19. Neurological and neuropsychiatric manifestations and their neuropathology

The most frequently reported neurological manifestations in patients infected with the SARS-CoV-2 coronavirus are headache (6%-15%), anosmia (41.0%), and ageusia (38.2%). The headache is described as generalized, hemicranial, or occipital of the oppressive type and which increases with physical activity or head movements, characteristics suggesting valsalva effect and therefore cerebrospinal fluid flow dysfunction and periarterial and perivenous cerebral glymphatic system dysfunction[1-3]

Deterioration of consciousness has been reported in up to 14.8% of cases of COVID-19 complicated with ARDS or Multiple Organ Dysfunction in the report by Mao et al., or as agitation in 69% of the cases and confusion in 45% of patients with post-intubation ARDS. Symptomatology that could correspond to delirium due to multiple causes: sedative drug effects, intubation with prolonged assisted ventilation, hypoxic, or metabolic encephalopathy[4,5]. Ischemic cerebrovascular disease has been reported in between 2.8% and 16.7%, encephalopathy with epileptic seizures 0.5%.[6] Five cases of Guillain-Barre syndrome were reported among 1200 cases of patients with COVID-19 in Italy[7]. In the United Kingdom out of 125 patients: cerebrovascular disease 57 (45.6%) ischemic, 9 (7.2%) hemorrhagic, 9 (7.2%) unspecified encephalopathy, 7 (5.6%) encephalitis, 10 (8%) psychosis, 6 (4.8%) neurocognitive disorder, and 4 (3.2%) affective disorder[8].

The presence of vasculitis/endotheliitis of small vessels with microhemorrhages and microinfarcts without damage to the large supra-aortic or intracerebral vessels has been reported in some cases (Figs. 1 and 2)[9]. However, two meta-analysis studies by stroke and COVID-19 report that elderly patients with elevated levels of D-dimer are associated with occlusion of the great vessels and increased mortality rates[10,11].

It is not yet clear whether SARS-CoV-2 is neurotropic in humans. Viral neuroinvasion could be achieved in a variety of ways, including trans-synaptic transfer through infected neurons, entry through the olfactory nerve, by the cribriform plate of the ethmoid bone to the glymphatic system with infection of astrocytes, infection of the vascular endothelium, or migration of leukocytes across the blood-brain barrier with manifestations of the central or peripheral nervous system (Table 1)[12-14].

Incidence and mortality, by age and gender, of COVID-19

According to the information provided by the WHO mission in China, from the first 41 cases reported between December 8, 2019, and January 2, 2020, it extended to 86,889 confirmed cases as of July 28, 2020, and 89,827 COVID-19 cases as of August 28, 2020. The median was 51 years of age with a majority of cases (77.8%) between 30 and 69 years of age, 51% of these cases were male. On May 28, 2020, a worldwide pandemic was reported with 5,808,946 and by June 28, 10,115,912 with 501,206 deaths, with a 6.4% fatality rate. On 28 July 2020, 16,662,462 positive cases were reported with 658,861 cumulative deaths and 24, 649, 431 COVID-19 cases as of August 28, with 835, 793 cumulative deaths. On September 28, 2020, were reported 33,034,598 with 996,342 deaths and by October 28 were 44,481,667 positive COVID-19 cases with 1,172,086 cumulative deaths. A global of 82,777,305 cases and 1,806,155 deaths were reported on December 31, 2020.

In the Americas, the crisis has not yet reached its critical point, with the United States being the most affected country in the region and also in the world, since as of July 28, 2020, there were 4,347,717 positive COVID-19 cases and 149,209 deaths reported, figure that increases to 11,715,316 positive cases for COVID-19 with 252,535 deaths as of November 20, 2020 (Table 2). By December 31, 2020, the number of accumulated positive cases rose to 19,744,734 and 342,395 people died[15].

In Mexico, the first case of a person with imported COVID-19 was reported on February 28, 2020. The Mexican Ministry of Health and CONACYT (National Council for Science and Technology) reported on May 28, 2020: 81,400 confirmed cases of COVID-19 with 9044 deaths and in 1 month, June 28, 2020, it almost tripled with 216,852 cases with 26,648 deaths. By July 28, 2020, there were 402,697 cases positive for COVID-19, 53.31% male and 46.69% female, of which 72.37% were outpatient and 27.63% were hospitalized, reporting 44,876 cumulative deaths, predominantly male. On August 28, 2020, 6 months after the first positive COVID-19 case in Mexico, were reported 585,738 confirmed cases, with a cumulative fatality of 63,146 people. On September 28 were reported 733,717 with 76,603 deaths, by October 28, 2020, were 906, 863 positive COVID-19 cases, with a cumulative deaths rate of 90,309. On 20 November 2020, 1,025,969 cases, 51% male and 48.94% female, with 100,823 deaths (Table 3). And as of December 31, 2020, the total accumulated number of positive cases reported was 1,426,094 and 125,807 deaths[16].

Table 1. Neuropathogenesis and neurologic manifestations of the central or peripheral nervous system in positive COVID-19 patients

Clinical entity	Signs and symptoms	Laboratory and cabinet	Pathogenesis
Encephalopathy	Altered mental state	MRI: Non-specific EEG: Diffuse slowing CSF: Normal CSF SARS-CoV-2 RT-PCR: Negative	Multiple Organ Dysfunction. Hypoxemia. Systemic inflammation. Endotheliitis
Encephalitis	Altered mental status and Central Nervous System Dysfunction	MRI: Non-specific EEG: Diffuse and focal Slowing CSF: Abnormal Pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Negative	Inflammation of the Central Nervous System
Viral encephalitis	Fever, altered mental status and Central Nervous System Dysfunction	MRI: Focal or multiple abnormalities EEG: Diffuse and focal Slowing CSF: Abnormal pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Positive Brain tissue: Positive Antigen or RNA	Viral invasion to the brain parenchyma
Viral meningitis	Fever, Headache with stiff neck, Kernig/Brudzinski positive	MRI: Non-specific EEG: Normal or focal abnormal CSF: Abnormal Pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Positive	Subarachnoid viral invasion
Anosmia and/or Augesia	Loss of smell/loss of taste	Clinical tests for assessing smell and taste: Abnormal	Viral invasion, peripheral or central?
Cerebrovascular disease	Focal motor or sensory neurological deficit	MRI: Ischemia or hemorrhage Laboratory: Increased markers of inflammation and abnormal coagulation factors	Coagulopathy
Acute disseminated encephalomyelitis	Headache, disorientation, acute neurological deficit with psychiatric manifestations	MRI: Hyper intensive lesions in Flair with supratentorial and subcortical predominance. CSF: Normal or with ↑ Proteins	Viral post-infection
Guillain-Barre syndrome	Ascending symmetrical flaccid muscle weakness with areflexia and pain	CSF: Cells 0-5 (Normal) + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Negative. Conduction velocity and electromyography: Abnormal	Viral post-infection
Muscular lesion	Myalgia	CPK: Elevated	Myopathy or Myositis?
Encephalopathy	Altered mental state	MRI: Non-specific EEG: Diffuse slowing CSF: Normal CSF SARS-CoV-2 RT-PCR: Negative	Multiple organ dysfunction. Hypoxemia. Systemic inflammation. Endotheliitis
Encephalitis	Altered mental status and Central Nervous System Dysfunction	MRI: Non-specific EEG: Diffuse and focal slowing CSF: Abnormal Pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Negative	Inflammation of the Central Nervous System.
Viral encephalitis	Fever, altered mental status and Central Nervous System Dysfunction	MRI: Focal or multiple abnormalities EEG: Diffuse and focal slowing CSF: Abnormal pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Positive Brain tissue: Positive antigen or RNA	Viral invasion to the brain parenchyma
Viral meningitis	Fever, Headache with stiff neck, Kernig/Brudzinski positive	MRI: Non-specific EEG: Normal or focal abnormal CSF: Abnormal pleocytosis + + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Positive	Subarachnoid viral invasion

(Continues)

Table 1. Neuropathogenesis and neurologic manifestations of the central or peripheral nervous system in positive COVID-19 patients *(Continued)*

Clinical entity	Signs and symptoms	Laboratory and cabinet	Pathogenesis
Anosmia and/or Augesia	Loss of smell/loss of taste.	Clinical tests for assessing smell and taste: Abnormal	Viral invasion, peripheral or central?
Cerebrovascular disease	Focal motor or sensory neurological deficit	MRI: Ischemia or hemorrhage Laboratory: Increased markers of inflammation and abnormal coagulation factors	Coagulopathy
Acute disseminated encephalomyelitis	Headache, disorientation, acute neurological deficit with psychiatric manifestations	MRI: Hyper intensive lesions in Flair with supratentorial and subcortical predominance. CSF: Normal or with ↑ Proteins	Viral post-infection
Guillain-Barre syndrome	Ascending symmetrical flaccid muscle weakness with areflexia and pain	CSF: Cells 0-5 (Normal) + ↑ Proteins CSF SARS-CoV-2 RT-PCR: Negative. Conduction velocity and electromyography: Abnormal	Viral post-infection
Muscular lesion	Myalgia	CPK: Elevated	Myopathy or Myositis?

Table 2. COVID-19 Pandemic.

Country	COVID-19 + Cases	Deaths	%	C/100,000
United states of America	11, 715, 316	252, 535	2.15	77.19
India	9, 004, 365	132, 162	1.46	9.77
Brazil	5, 981, 767	168, 061	2.80	80.23
France	2, 137, 096	47, 201	2.20	70.46
Russia	1, 998, 966	34, 525	1.72	23.90
Spain	1, 541, 574	42, 291	2.74	23.79
United kingdom	1, 456, 940	53, 870	3.69	81.02
Argentina	1, 349, 434	36, 532	2.70	82.10
Italy	1, 308, 528	47, 870	3.65	79.21
Colombia	1, 225, 490	34, 761	2.83	70.01
Mexico	1, 019, 543	100, 104	9.81	79.33
China	91, 935	4, 742	5.15	0.34

Global cases: 58, 014, 491. Global deaths: 1, 378, 866. Accumulated cases and deaths by country as of November 20, 2020.

Risk factors for COVID-19 lethality

The risk factors increase the possibility of Acute Respiratory Distress Syndrome (ARDS) and death for patients who are infected with the new coronavirus SARS-Cov-2 are:

1. Age and Gender

The number of COVID-19 positive patients who are asymptomatic is unknown, with percentages ranging from 3% to 6%. Of the symptomatic patients, 26% have mild uncomplicated disease (Phase I), 65% have moderate to severe symptoms (Phase II), and only 9% have severe symptoms that are complicated by pneumonia that progresses to ARDS or Multiple Organ Dysfunction (Phase III) (Table 4).

In multiple logistic regression, the male sex was associated with severe symptoms (odds ratio [OR] 2 5 [IC 95% 1 1-6 [1]). The probability of severe symptoms increased slightly with age, although only people with 60-69 years of age had a significantly higher risk compared to the baseline category, people with 50-59 of age (OR 3 4 [95% 1 4-9 [5]). Males accounted for 63.7%[17,18].

In Mexico, the reported case fatality as of June 28, 2020, represents 12.28% with 26,648 of the 216,852 positive COVID-19 cases. Males predominate with a 66% (17,569) versus a 34% (9,079) female. The age group of 92.65% is over 40 years of age. By July 28, 2020, the total number of cumulative deaths was 44,876, 64.94% male and 35.06% female. On August 28, 585,738 positive COVID-19 cases, 52.52% men, 47.49% women, were reported with 63,146 deaths, 64.43% men, 35.57% women, with a rate per 1000 cases of 38.24-44.05 between 70 and 99 years of age, compared to 0.92 in those under 29 years of age, 76,603 deaths by September 28, 90,309 cumulative deaths by October 28, 2020, and 100,823 on November 20, 2020, 63.74% male and 36.26% female (Fig. 3).

Table 3. COVID-19 in Mexico. Cumulative cases and deaths from February 28, 2020 to November 20, 2020

Ciudad de México	184,636	16,770	Sinaloa	23,308	3,848
Estado de México	104,341	11,443	Guerrero	23,112	2,335
Nuevo León	61,545	4,384	Yucatán	22,931	2,005
Guanajuato	55,967	3,730	Durango	18,212	1,017
Sonora	41,118	3,340	Querétaro	17,804	1,369
Veracruz	38,549	5,147	Hidalgo	17,638	2,543
Jalisco	38288	4,568	Quintana Róo	13,992	1,885
Coahuila	38,279	3,029	Zacatecas	13,828	1,159
Puebla	38,215	5,037	Baja California Sur	13,684	650
Tabasco	36,075	3,100	Aguascalientes	11,217	1,007
Tamaulipas	34,014	2,917	Tlaxcala	8,872	1.193
San Luis Potosí	32,267	2,308	Chiapas	7,657	1,088
Michoacán	27,150	2,167	Morelos	7,404	1,271
Chihuahua	26,974	3,035	Nayarit	6,997	911
Baja California	24,840	4,098	Colima	6,963	785
Oaxaca	23,455	1,783	Campeche	6,673	901
Total				1,025,969	100,823

Table 4. Severity Levels and Evolution of COVID-19

Severity levels and evolution	Clinical, laboratory and radiological findings
Phase I - Uncomplicated disease	Fever, rhinorrhea, odynophagia, cough, myalgia, and headache
Phase II or pulmonary phase - Mild pneumonia	Confirmed with chest X-ray or CT scan (CO-RADS 2-3). SaO_2 >90%. RT-PCR +
- Severe pneumonia	Severe pneumonia Fever, productive cough, dyspnea. Chest CT scan (CO-RADS 4-5). SaO_2 <90% and tachypnea ≥ 30/minute. RT-PCR + IgM +, IgG + Lymphopenia $<0.8\times10^9$/L. Thrombocytopenia $<100\times10^9$/L D-dimer elevation >1 µg/L. PCR elevation Ferritin elevation >300 µg/L IL-6 elevation >7.4 pg/mL Procalcitonin elevation ≥0.5 ng/mL
Phase III or hyper-inflammatory phase - Acute Respiratory Distress Syndrome (ARDS)	Cough, dyspnea. Chest CT with bilateral ground-glass opacities, with hypoxia: - Mild: 200 mmHg $<PaO_2/FiO_2 \leq 300$ - Moderate: 100 mmHg $<PaO_2/FiO_2 \leq 200$ - Severe: $PaO_2/FiO_2 \leq 100$ mmHg
- Multiple Organ Dysfunction Syndrome by Septicemia	Organic dysfunction on the SOFA Score > 2 points or an acute change in the Quick Sofa with > 2 criteria
- Septic shock	Arterial hypotension that persists despite volume replacement with solutions and requires vasopressors to maintain MAP ≥65 mmHg and lactate ≥ 2 moll/L (18 mg/dL) in the absence of hypovolemia.

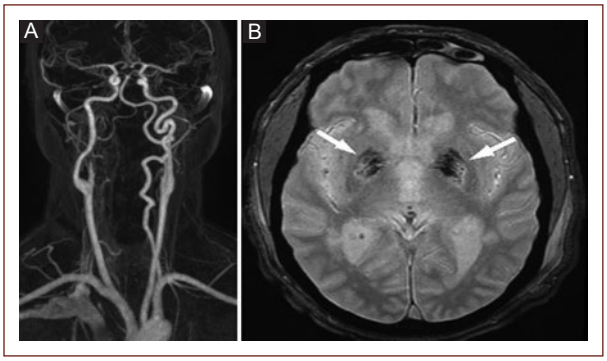

Figure 1. A: 3D coronal reconstruction of supra-aortic and intracerebral vessels **(B)** T2 brain MRI with microhemorrhages in both pale globe.

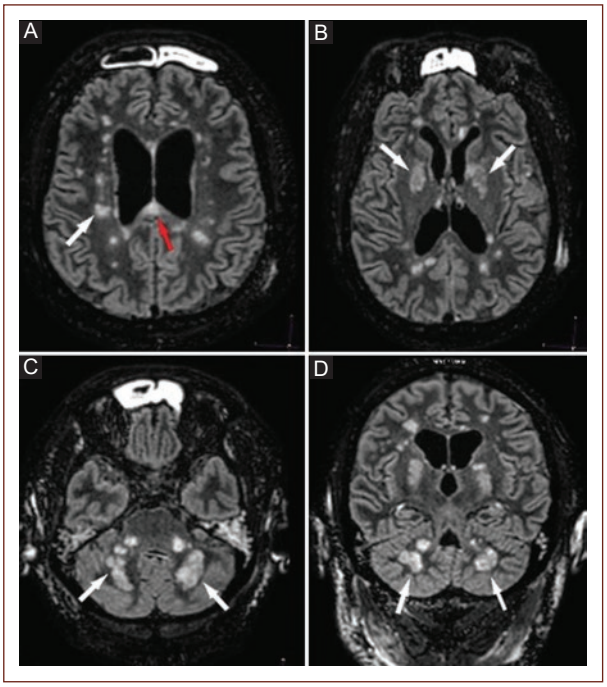

Figure 2. Axial **(A, B, and C)** and coronal **(D)** Flair MRI. Diffuse hyperintense images suggestive of ischemic lesions in basal ganglia and cerebellar peduncles.

2. Obesity, type 2 diabetes mellitus, and systemic arterial hypertension

An age of over 65 years and the male gender are risk factors for critical complication in patients infected with the new coronavirus SARS-CoV-2, but comorbidities also increase the risk of lethality in patients with C0VID-19. Richardson et al. reported in 5700 patients in New York City, the presence of Arterial Hypertension in 3026 (56.6%), Obesity with a Body Mass Index (BMI) greater than 35 in 1737 people (41.7%), Diabetes mellitus in 1808 (33.8%), and Sleep Apnea in only 154 patients (2.9%).[19] Out of a group of 124 people in France with COVID-19, 85 patients (68.6%) required assisted mechanical ventilation (AMV), and the OR in cases requiring AMV with BMI > 35 kg/m^2 versus patients with BMI <25 kg/m^2 was 7.36 (95% CI 1.63-33.14) regardless of age, diabetes, or arterial hypertension[20].

In Mexico, the Ministry of Health reports on November 20, 2020, that in 1,025,969 positive cases for C0VID-19, 51.06% were male and 48.94% female, arterial hypertension was in 20.09%, obesity 19.59%, diabetes mellitus 16.44%, and smoking 7.77%. In the critical group with the death of 100,823 people (9.82%), 63.74% were of the male gender and 36.26% of the female gender, arterial hypertension was present in 45.38%, diabetes mellitus in 38.58%, obesity in 23.90%, and smoking in 8.73% of the cases.

Bello-Chavolla et al. in a retrospective analysis of 15,529 SARS-Cov-2 positive patients compared to 46,960 SARS-Cov-2 negative persons found: obesity in 3,215 (20.7%) versus 6,570 (14%), respectively, arterial hypertension in 3,370 (21.7%) versus 7353 (15.7%), and diabetes mellitus in 2,831 (18.2%) versus 5,163 (11%). Considering that the coexistence of two comorbidities such as obesity and diabetes mellitus, particularly of early onset, increases the risk of severe complications in patients with COVID-19 (Fig. 4)[21].

Treatment of COVID-19

The COVID-19 pandemic represents the largest global public health crisis of this generation and potentially since the outbreak of the pandemic influenza in 1918. The speed and volume of clinical trials launched to investigate possible therapies for COVID-19 highlight both the need and the ability to produce high-quality evidence even in the midst of a pandemic. Therapies have not been proven to be effective to this date and current prevention and treatment recommendations are very similar to those suggested in 1918[22-24].

Prevention

Frequently washing hands with soap and water for at least 20 s or using 70% alcohol-based gel solutions. When coughing or sneezing, the use of sneeze etiquette, which consists of covering the nose and mouth with a tissue or the inside angle of the arm. No spitting, and if necessary, use a tissue, put it in a plastic bag,

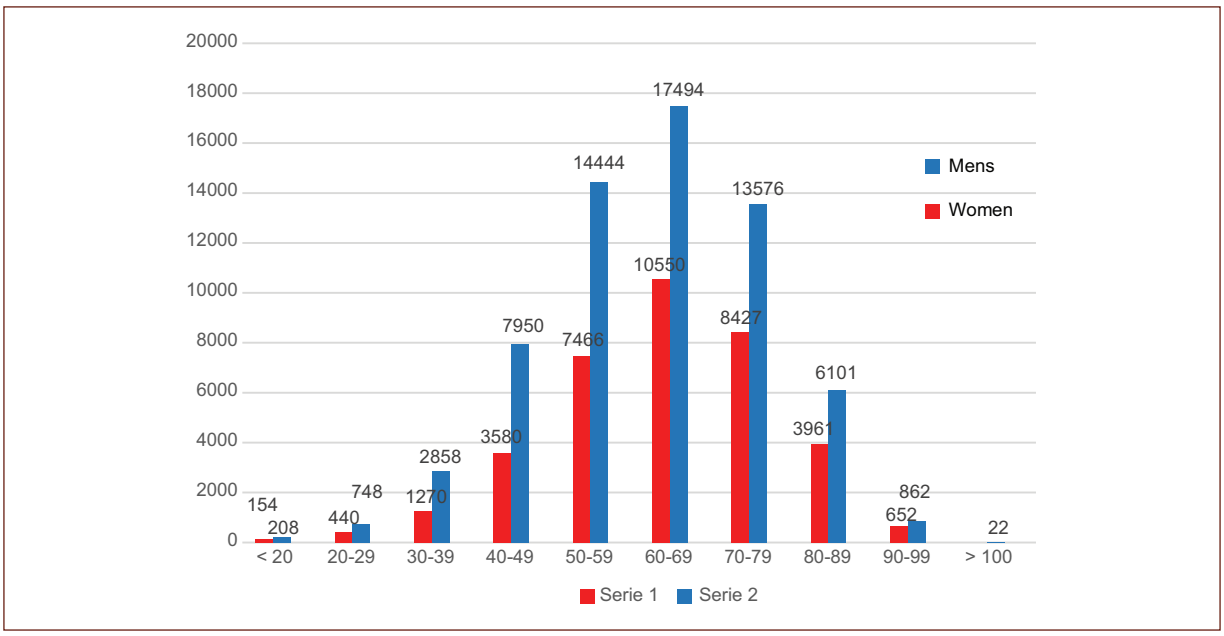

Figure 3. COVID-19 Mexico. Cumulative deaths by age and gender. Total: 100,823 February 28 to November 20, 2020.

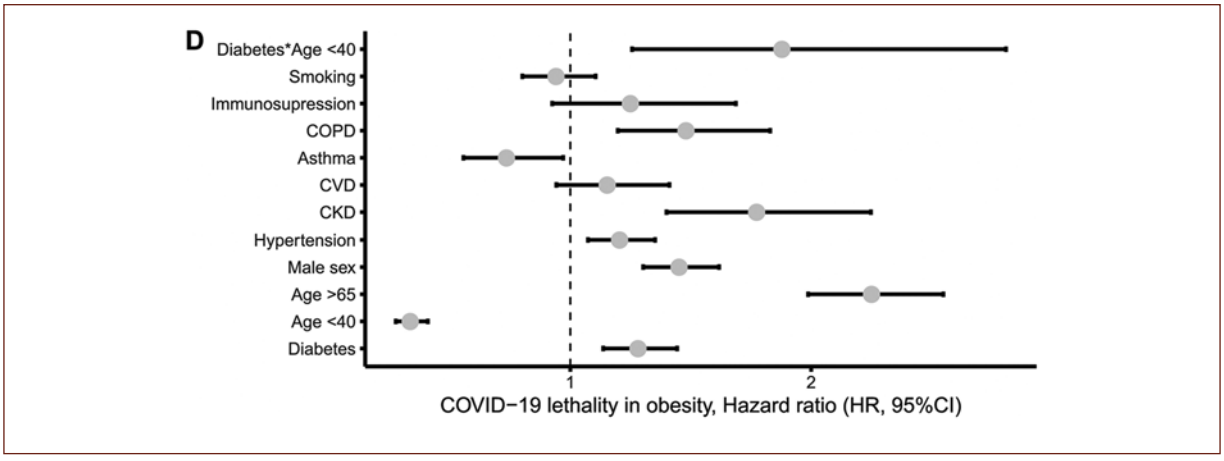

Figure 4. Comorbidities and Lethality of COVID-19 in Mexico (HR, 95%CI).

tie it up and throw it away, then wash hands. No face touching with dirty hands, especially the nose, mouth and eyes. Maintain a social distance of at least one meter. Clean and disinfect surfaces and objects of common use in houses, offices, closed spaces, transportation, meeting centers, etc., ventilating and allowing sunlight to enter. Staying at home, according to the health recommendations of each entity. Seek medical attention if any of the symptoms are present (fever over 38°C, headache, sore throat, runny nose, etc.). Avoid contact as much as possible with people who have respiratory diseases. If you need to leave your home, wear a mask that covers your mouth and nose to reduce the risk of infection (Fig. 5).[25] As of November 10, 2020, there are 11 vaccine study protocols for COVID-19 in phase III like that of the University of Oxford/Astra Zeneca.[26] In December 2020, those of Biontech/Fosun Pharma/Pfizer and Moderna/NIAID were approved by the FDA. Pfizer's two-dose regimen vaccine (BNT12622b2) is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS CoV-2 full-length spike protein that conferred 95% protection

Figure 5. Recommendations on preventing SARS-CoV-2 infection, 2020.

against COVID-19 in persons 16 years of age or older[27].

Convalescent plasma in the management of COVID-19 was not associated with a reduction in progression to severe COVID-19 or all-cause mortality (PLACID Trial)[28,29].

Proposed pharmacological treatment

Antimalarial drugs such as hydroxychloroquine and chloroquine have been proposed and showed some benefit in patients with SARS-CoV in 2002, (quinine was used in the 1918 influenza pandemic), protease inhibitor drugs such as lopinavir and ritonavir, RNA polymerase inhibitors such as remdesivir, ribavirin, or favipiravir, interferons such as the ß-1b interferon, interleukin-6 (IL-6) receptor monoclonal antibody such as tocilizumab, interleukin-1(IL-1) receptor monoclonal antibody such as anakinra, drugs that prevent the introduction of SARS-CoV-2 to the host cell such as umifenovir (arbidol), and others such as nitazoxanide that induces the host cell's interferon response or an antiparasitic such as ivermectin with broad-spectrum antiviral activity[30].

- The evidence on the effectiveness of chloroquine and hydroxychloroquine, in addition to being contradictory, is scarce and of low quality. One clinical trial reports that hydroxychloroquine decreases clinical recovery time by 2 days, while another reports no difference in viral clearance between patients receiving and not receiving the anti-malarial.[31] The included systematic reviews have contradictory conclusions, but all of them show the low quality of the evidence, one of these studies even published a retraction due to errors in the methodology[32].

An important precaution is that the combined use of antimalarials with azithromycin, lopinavir/ritonavir, and remdesivir has been associated with an increased risk of a prolonged QTc interval and arrhythmias. Recently Geleris et al. report an observational study in New York that does not recommend the use of hydroxychloroquine in patients with COVID-19 complicated with ARDS[33].

The evidence on antiviral therapy with lopinavir/ritonavir, oseltamivir, and ganciclovir in patients with severe COVID-19 is weak and contradictory, and its effectiveness in decreasing the risk of progression to ARDS and reducing mortality is unclear. Drugs such as ivermectin and tocilizumab have low quality observational studies that do not allow us to assess the effectiveness and safety in patients with COVID-19[34,35].

A recent double-blind controlled study of remdesivir against placebo reports a benefit in patients with COVID-19 in preventing a statistically significant percentage of ARDS complications by administering an initial dose of 200 mg intravenous remdesivir and 100 mg every 24 h over the next 9 days[36]. However, a subsequent randomized study to evaluate the benefit of remdesivir showed no significant difference between remdesivir and placebo, evaluating results at day 5 and day 10 of treatment[37], and the conclusions of the WHO SOLIDARITY study report that remdesivir, hydroxychloroquine, lopinavir, and interferon have little or no effect on hospitalized COVID-19[38].

Reyes et al. reported in December 2020 the use of colchicine 0.5 mg orally per day, as a nonsteroidal anti-inflammatory therapy that inhibits E-selectin and L-selectin as well as NLRP3 preventing cytokine storm and platelet aggregation. The use of colchicine, in this randomized, double-blind study against placebo in COVID-19 positive patients, reduced the risk of hospitalization by 25%, mechanical ventilation by 50%, and death by 47%[39].

- Two observational studies report beneficial effects of glucocorticoid use in patients with a serious COVID-19 disease and a systematic review and meta-analysis on clinical outcomes of the use of corticosteroid in patients with COVID-19 suggesting that its use at low or moderate doses reduces the possibility of mild/moderate to severe disease progression, and mortality[40-42].
- Both the Wuhan University guide and the Surviving Sepsis guidelines recommend oxygen therapy as needed according to hypoxia. It is recommended to start with a nasal cannula and progress to high flow oxygen sources.

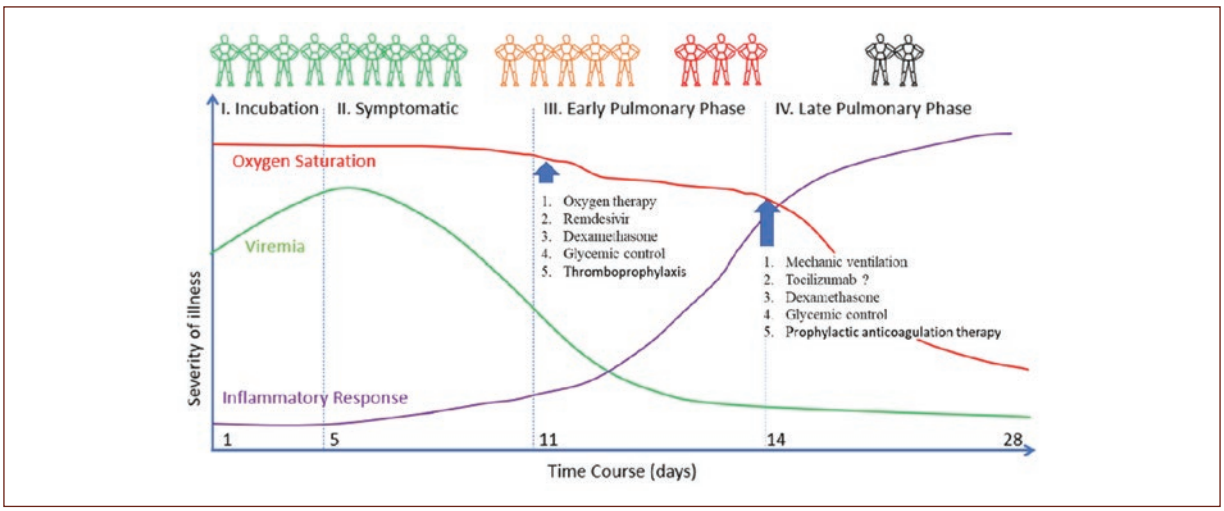

Figure 6. COVID-19. Evolution y proposed treatment.

- The two guidelines included recommend restrictive resuscitation with intravenous fluids (mainly crystalloids), both in ventilated and non-ventilated patients. The use in high volumes may worsen the degree of pulmonary edema, prolong days on the ventilator, ICU stay, and mortality in patients with ARDS. (Fig. 6)[43,44].

It is clear that the pathogenesis of COVID-19 involves not only virus replication but also immunomodulation and inflammation. Sequential studies of biomarkers such as interleukin-6, C-reactive protein, ferritin, and D-dimer should help us to better understand the pathogenesis of COVID-19. Combination therapy studies with other antivirals and dexamethasone in appropriate sequence are a high priority, and plans for such studies are already underway.

Sleep associated breathing disorders such as obstructive sleep apnea syndrome (OSAS) and Sleep-Related Hypoventilation Syndromes have not been considered as risk factors in the complication of SARS-CoV-2 infection and that may contribute to the progression from a mild COVID-19 illness to a severe or critical phase with ARDS, including death.

Adult Obstructive Sleep Apnea Syndrome

Diagnostic criteria for OSAS in adults: Criteria A and B must be met[45].

A) The presence of one or more of the following:
1. The patient complains of daytime sleepiness, non-restorative sleep, fatigue, or insomnia.
2. The patient wakes up due to shortness of breath, choking, or suffocation.
3. Bed partner reports habitual snoring and breathing pauses in the patient during sleep.
4. The patient has been diagnosed with arterial hypertension, presents mood disorders, cognitive dysfunction, coronary artery disease, ischemic cerebrovascular disease, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.

B) The polysomnography (PSG) record shows (Fig. 7):
1. Five or more predominantly obstructive respiratory events (obstructive apnea, mixed apneas, hypopneas or respiratory effort related arousals [RERA] per hour of sleep during a PSG or hourly events performed outside a sleep clinic with limited number of channels).

Or:

C) PSG or monitoring (OCST: out of center sleep testing) demonstrates:
1. Fifteen or more predominantly obstructive respiratory events (apnea, hypopneas, and RERAs) per hour of sleep during a PSG or for 1 h of OCST monitoring.

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is characterized by repeated episodes of complete (apnea) or partial (hypopnea) upper airway obstruction that occurs during sleep.

These events result in reduced blood oxygen saturation and usually end in brief, transitory awakenings. By definition, episodes of apnea or hypopnea last a minimum of 10 s. Most events last from 10 to 30 s, but sometimes they persist for a minute or more. These events can occur at any stage of sleep, but most often in stages N1, N2 of non-REM sleep, and R (REM sleep). During REM sleep or when the person is sleeping in

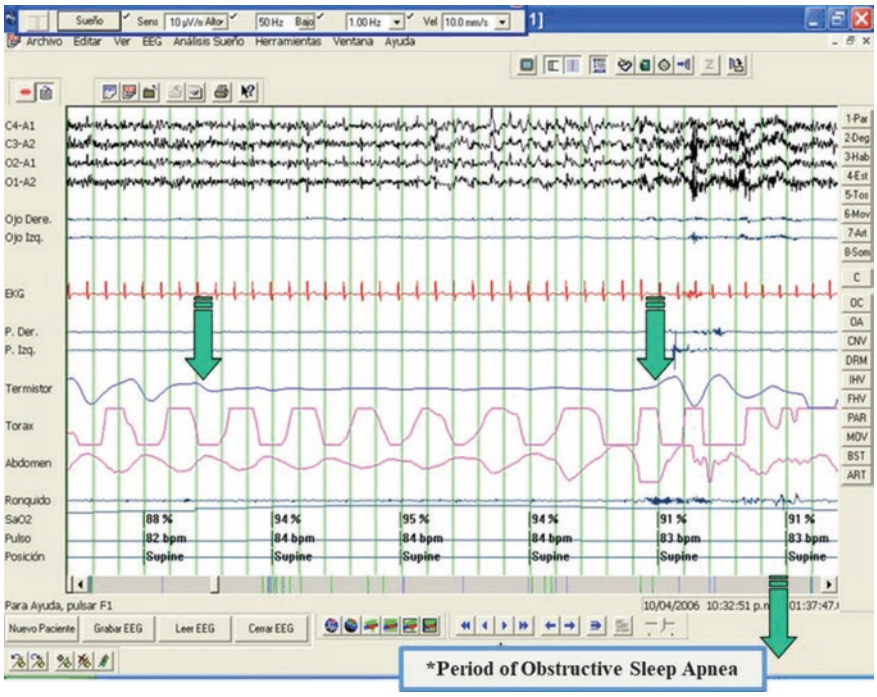

Figure 7. PSG of an obese adult patient, with controlled arterial hypertension, excessive daytime sleepiness, and loud snoring during sleep.

the supine position, events are usually longer and associated with a severe decrease in oxygen saturation.

Oxygen saturation usually returns to normal after normal breathing resumes, but may remain low if apnea or hypopnea events are very frequent and prolonged or if there is underlying lung disease. The prevalence of OSAHS has increased to 30% from 1990 to 2010, from 4% in men and 2% in women to 7.5% in men and 4.2% in women. Age is also an important factor. As OSA is most common after age 40 and reaches its peak frequency in individuals over 60 years of age[46].

Given that obesity is the main risk factor for the development of OSA, it is expected that as the Mexican population continues to suffer from the severe overweight pandemic considering the BMI (Body Mass Index = mass/height² = per kg/m²: BMI kg/m² > 25.00), obesity (BMI kg/m² > 30.00) and morbid obesity (BMI kg/m² > 40.00), the incidence and prevalence figures of OSA will also increase.

One parameter to consider in addition to BMI is the perimeter of the neck, as the larger the perimeter, the greater the risk of a higher apnea/hypopnea index (AHI) in people with OSAHS. That is, in women with a neck circumference greater than 38 cm and in men with more than 40 cm, the frequency of OSA is higher in these subjects[47].

Hypoxia and the changes in sympathetic activity associated with OSA originate: insulin resistance with increased adipokines such as leptin and adiponectin related to pro-inflammatory cytokines such as interleukin-6 (IL-6), the monocyte chemoattractant protein (MCP-1), plasminogen activator inhibitor-1 (PAI-1), or tumor necrosis factor alpha (TNFα), favoring endothelial dysfunction with systemic arterial hypertension, metabolic syndrome, coronary artery disease, or ischemic cerebrovascular disease[48-50]

Therefore, patients with OSAS have a higher risk of presenting these comorbidities, with an OR for arterial hypertension of 2.89 and for cerebrovascular disease the OR is of 1.58. On the other hand, the most frequent sleep disorder in post-cerebral infarction is OSA with a 62% on the first night[51].

The general treatment for OSA is hygienic and dietary measures such as: weight loss, avoiding the use of tobacco, and alcohol or benzodiazepine abuse. Specific treatment is with CPAP (nasal continuous positive airway pressure) which lowers the apnea/hypopnea index (AHI) and prevents chronic nocturnal hypoxemia with decreased superoxide production, and ROS,

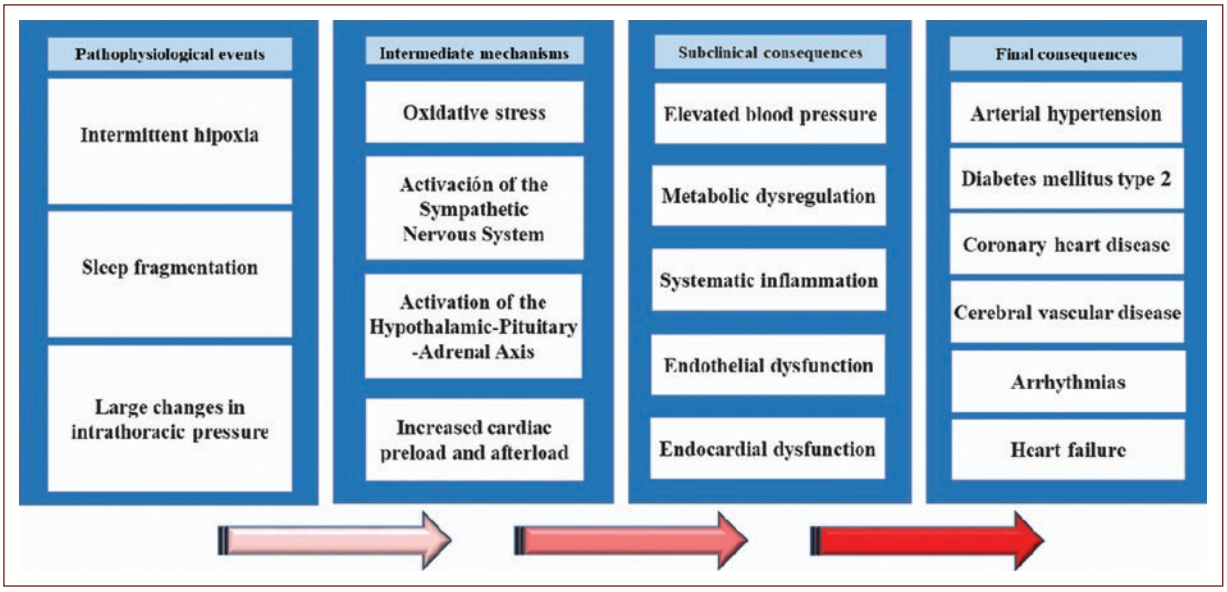

Figure 8. Putative causal mechanisms of metabolic and cardiovascular diseases related to obstructive sleep apnea (OSA).

decreasing endothelial adhesion molecules such as intercellular molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), interleukin-6 (IL-6), and increasing nitric oxide (NO) levels[52].

Obesity, OSAS, and Endothelial Dysfunction

Endothelial and metabolic dysfunctions as well as adiposity constitute physiopathological links between an unfavorable lifestyle and the so-called classic and emerging risk factors, among which are arterial hypertension, dyslipidemia, diabetes mellitus, activation of the inflammatory cascade, the prothrombotic state, and a substrate that favors cardiac arrhythmias. Among the subclinical and final consequences the role of overweight and obesity stands out, which reflect visceral adiposity as a central element in the risk and pathogenesis of endothelial dysfunction leading to coronary artery disease, ischemic cerebrovascular disease, and most probably in the complication of COVID-19 favoring a hyperinflammatory reaction to the SARS-CoV-2 response and the immune response with pyroptosis and cytokine storm originating an increase in the exudate at alveolar level with vascular endotheliitis and pulmonary thrombosis (Fig. 8).

Visceral fat is considered a mere energy deposit with a wide anatomical distribution. In recent years, it has become clear that visceral fat tissue is a true endocrine organ of great activity producing adipokines that intervene in different events that can lead to the development of a metabolic syndrome. Insulin resistance is, for example, a key situation in the progression of the disease and different adipokines induce this resistance directly, such as leptin, resistin, TNFα, and IL-6, by preventing the transduction of the signal produced by insulin, thus inhibiting the transcription and translocation of glucose receptors. The resulting hyperglycemia leads to an increase in the inflammatory process due to the production of reactive oxygen species (ROS)[53,54] (Fig. 9).

At the same time, secondary hyperinsulinemia to such resistance causes defects in phagocytic cells by increasing the circulation of bacterial antigens, which have the capacity to activate leukocytes and adipocytes that then release pro-inflammatory cytokines, this being another causal mechanism of inflammation[55-57].

Consequences will be increased in patients with COVID-19, if obesity is associated with OSAS or Sleep-Related Hypoventilation Syndromes (Fig. 10). At present, there is no direct evidence to support OSA as an independent risk factor for severe SARS-CoV-2 infection, but some inferences can be made from the data on ARDS. Obesity was shown to be an independent risk factor for developing ARDS among hospitalized patients. In a retrospective study of more than 6,000,000

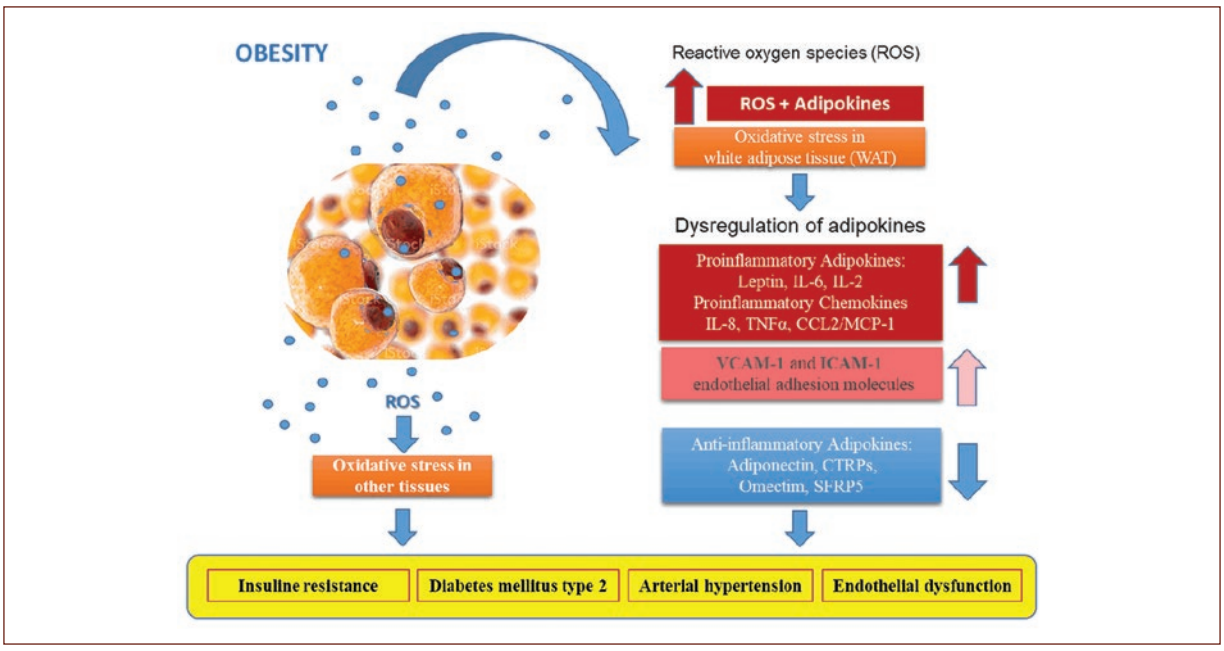

Figure 9. Increased oxidative stress in obesity.

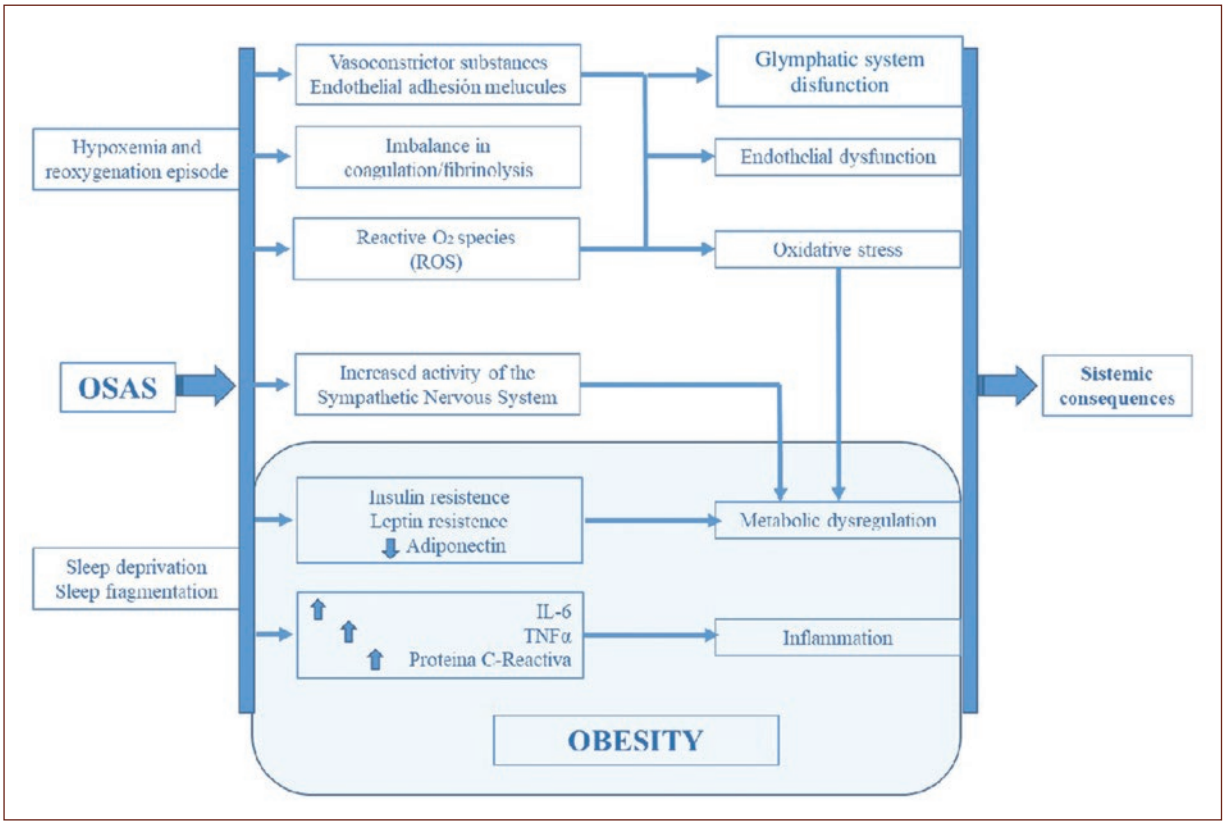

Figure 10. Consequences of the combination of OSAS with obesity. OSAS: Obstructive sleep apnea syndrome; ROS: reactive O2 species; TNF-α: tumor necrosis factor alfa.

cases, obstructive sleep apnea has been associated with an increased risk of developing ARDS among patients undergoing surgical procedures. In addition, OSA patients who are hospitalized generally have an increased risk of mortality and morbidity, but the risk is decreased among patients treated with noninvasive ventilation (NIV)[58,59].

Conclusions

Hypoxia due to inflammation of the upper airway or lower airway in patients infected by SARS-CoV-2, obesity with or without obstructive sleep apnea (OSA) in the elderly and OSA with dysfunction cerebral glymphatic system during sleep are severe factors that can contribute to the transition from phase I of COVID-19 to Phases II and III with hyperinflammation, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, and death. We, therefore, consider the need to carry out prospective clinical studies supported by ambulatory polysomnography and in the shorter term, retrospective studies, to have information based on evidence medicine on the level of risk of OSA in comorbidity and fatality associated with COVID-19.

Hence, we propose to disseminate worldwide the need to question, in patients with initial COVID-19, the history of chronic snoring, the possibility of pauses in breathing during sleep reported by the patient's partner and the presence of excessive daytime sleepiness. Particularly in male patients over 60 years of age with obesity and/or diabetes, to have the clinical suspicion of OSA that can be corroborated with an outpatient polysomnography study and establish preventive treatment with colchicine as an anti-inflammatory measure and in case of increased frequency respiratory, dyspnea or O2 saturation less than 89%, indicate the use of non-invasive ventilation, during wakefulness but with greater emphasis during sleep.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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