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EDITORIAL

Individual health reflected in the collectivity

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It all started in December 2019, the authorities of the Chinese Health Services reported the presence of several cases of pneumonia in the city of Wuhan, China. The following month, the Shanghai Public Health Clinical Center and the School of Public Health, showed the complete genomic sequence of the 2019-nCoV warning of how this infection could affect not a few but thousands of individuals. The first reported case in the United States occurred in a young man who had visited Wuhan[1].

The most interest aspect is that person-to-person transmission is demonstrated and that an asymptomatic and healthy young woman with a positive real-time polymerase chain reaction test for COVID-19 who lives in Wuhan visited her family in the province of Anyang, China, and developed a cluster of familial pneumonia in an incubation period of 1-19 days[2].

Most of the cases have occurred in adult people 30-79 years (87%), and only 1% in people younger than 9 years of age. Furthermore, being in a city, it extended in just 30 days to all of China, February 18, 2020, reported 72,528 confirmed cases of COVID-19 (99% of the global total) and 1870 deaths (99.8% of the global total), with more than 3000 cases in health personnel. The sanitary measures were isolation, quarantine, social distancing, and community contention. By February 20, 2020, 1073 cases had already been reported outside of China[3].

On February 7, 2020, the WHO Scientific and Technical Advisory Group for Infectious Hazards issued a series of recommendations to try to stop the spread of COVID-19. They were emphasizing that although the transmission was possibly initially from animals (bat) to humans, it is clear that the spread is occurring by human-human transmission. Insisting that although the fatality is challenging to determine, the lung affection mainly like pneumonia, is the most critical (1-2%), although lower than for severe acute respiratory syndrome (10%). Transmission is possibly oral, so conglomerations should be avoided. Moreover, it also seems that the most affected are older adults with comorbidities. The WHO insists on the advisability of suspending public activities (especially with high attendance) and also closing schools, working remotely, making phone calls, and using telemedicine. Besides, they suggest maintaining and having the ventilatory support equipment, oxygen, and extracorporeal membrane oxygenation equipment to be ready for as soon as it is necessary to use[4].

In addition to the above, we must consider that just as animal-human and then human-human transmission occurred initially, human-animal (pets) transmission may also be feasible and thus further spread the problem[5].

Despite the measures taken by the Chinese government and the warnings issued by the WHO, cases of

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pneumonia began to appear in the Milan metropolitan area, which ended in a health problem that finally isolated the country entirely[6].

In an "invisible" spread, the problem grew and spread from Milan to Lyon, France, and Alitalia passengers arriving in Mauritius were quarantined. Some countries outside Europe began to reject passengers from Italy. Four people in the UK were confirmed positive for COVID-19 and had been on the Diamond Princess cruise. South Korea reported almost 1000 affected, and the problem continued to grow[7].

The problem in Italy began on January 31, 2020, with two Chinese visitors who were staying in a central hotel in Rome and had landed at Milan's Malpensa Airport on January 23. Just a month later, the Prime Minister of Italy declared the situation to be a national emergency[8].

As this is being written, COVID-19 Global Cases by the Center for Systems Science and Engineering at Johns Hopkins University reports 179,029 confirmed cases of COVID-19, 7057 deaths, and only 78,073 fully recovered[9]. The spread includes an increasing number of cases, from highest to lowest, in China, Italy, Iran, Spain, South Korea, Germany, France, the USA, the UK, and Holland.

Although this is only a partial view of what happened in a pandemic that has grown exponentially, it shows us that measures as old and simple as social isolation, quarantine, public containment, and keeping our hospitals ready for who requires them are vital measures. Measures that are needed to avoid problems that could massively affect a high percentage of the population.

It is evident in this brief story that the health of an individual in an infectious-contagious problem can affect an entire community. The preventive health measures taken by countries such as France, Spain, Italy, the United States, and, of course, China itself should be an example to all the nations. Therefore, we must apply what to do and what to avoid; apparent health does not seem to be enough, although older adults with comorbidities are the most susceptible. Let us hope that our health systems manage to be sufficient and adequate for a problem that can potentially affect all the populations of Latin America.

References

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. JAMA. 2020;323:707-8.
2. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. February 21, 2020 [Epub ahead of print].
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. February 24, 2020 [Epub ahead of print].
4. Heymann DL, Shindo N, WHO Scientific and Technical Advisory Group for Infectious Hazards. COVID-19: what is next for public health? Lancet. 2020;395:542-5.
5. Bonilla-DK BB, Rabaan A, Gomez WE, Rodriguez-AJ RR. Una nueva zoonosis viral de preocupación global: COVID-19, enfermedad por coronavirus 2019. Iatreia. 2020;33:107-10.
6. Spina S, Marrazzo F, Migliari M, Stucchi R, Sforza A, Fumagalli R. The response of Milan's emergency medical system to the COVID-19 outbreak in Italy. Lancet. 2020;395:e49-50.
7. Day M. Covid-19: surge in cases in Italy and South Korea makes pandemic look more likely. BMJ. 2020;368:m751.
8. Carinci F. Covid-19: preparedness, decentralisation, and the hunt for patient zero. BMJ. 2020;368:m799.
9. Available from: https://coronavirus.jhu.edu/map.html.

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EDITORIAL

External compression headache: A neglected headache

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External compression headache (ECH) is a scarcely studied headache. There are different possible causes, such as mechanical factors, hypoxemia, hypercapnia, or associates stress, or could even be a sum of these factors that lead to the origin of this headache. ECH is provoked by donning objects with tight bands or straps around the head and has been reported with the use of hats, helmets, frontal lux devices, headsets, goggles, and N95 face masks. At present, we are experiencing the pandemic caused by the severe acute respiratory syndrome by a coronavirus 2 (SARS-CoV-2), whose disease name is CoV disease 2019 (COVID-19). Due to this, the protection measures were extended among health care workers and the general population, such as the use of personal protective equipment (PPE), that will, expectedly, rise the incidence of this headache.

Headache due to external compression was incorporated into the international classification as external-pressure headache since the first edition of the International Classification of Headache Disorders[1]. According to the ICHD-3 in the heading 4: other primary headaches, to which the ECH belongs, the diagnosis is made by meeting the following criteria: at least two episodes of headache, brought on by and occurring within 60 min during continued pressure from something outside your body, maximal pain at the site of compression, and resolving within 1 h after compression is relieved[2].

The pathogenesis of ECH is still uncertain. Depending on the personal accessory used, there are different possible causes or could even be a sum of factors that lead to the origin of the headache. It could involve mechanical factors, hypoxemia, hypercapnia, or associated stress. The continuous pressure or tractional force from personal accessories may lead to local tissue damage and exert an irritative effect on the underlying superficial sensory nerves (trigeminal, occipital, and cervical nerves branches) that innerve the face, head, and cervical region[3]. Furthermore, the alveolar hypoventilation caused by prolonged use of face masks can lead to an increase in carbon dioxide with intra- and extracranial vasodilation (Fig. 1)[4,5].

ECH is provoked by donning objects with tight bands or straps around the head and has been reported with the use of hats, helmets, frontal lux devices, headsets, goggles, and more recently N95 face masks[6]. Besides, it is usually an occupational disease, because in different professions, the cause of the headache is the equipment they use to work, such as helmets or hats in policemen, firefighters, construction workers, military personnel, athletes, and aviation pilots, and the PPE that use the health care workers[7].

Usually, the pain of ECH is described as moderate in intensity, not impeding routine activities, frequently constant, consistent with the use of the accessories, of oppressive quality, more severe at the area where the object is pressing and tends to increase with the longer exposure to the compressing object. The pain is not associated with other symptoms and disappears shortly after removing the cause[3]. In patients with a pre-existing headache, there are two possibilities: one is that the prolonged external compression may lead to a more

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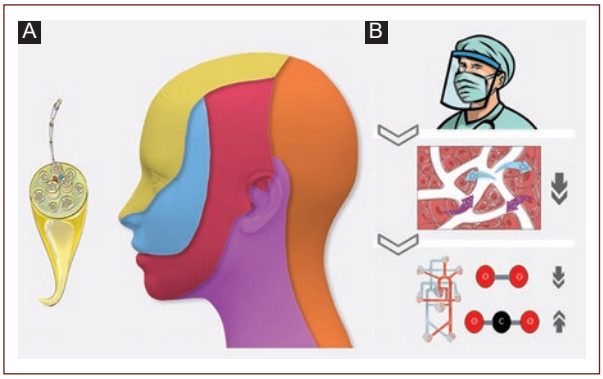

Figure 1. A: pressure or tractional forces from the objects may lead to local tissue damage and exert an irritative effect on sensory nerves (green area: ophthalmic nerve, blue area: maxillary nerve, purple area: mandibular nerve, yellow area: cervical nerves, pink area: superficial cervical plexus). **B:** prolonged use of face masks may lead to an alveolar hypoventilation that will cause hypoxemia and hypercapnia.

severe episode of the previous headache or that a *de novo* headache occurs with the previously described characteristics of ECH. For example, patients with previous migraine have reported the triggering of a more severe, pulsatile, unilateral headache with nausea/vomiting, photophobia, and phonophobia that did not end if the causal item was removed, requiring specific medical treatment[8].

Because these attacks disappear when the pressure is removed, seeking medical attention is often postponed so this headache is under-recognized. The current treatment is based on education to remove frequently and temporarily the headwear or traction that causes the pressure. Educational materials could be beneficial. The possibility of trying different styles and sizes of headgear may be useful for some of these exposed subjects, to get the most comfortable option. Moreover, the prevention would be skipping headwear (should it be possible) if you are predisposed to ECH.

In recent years, we have witnessed epidemics involving different strains of influenza, SARS, and Ebola, transmitted by direct or indirect contact and/or the respiratory route; therefore, the use of PPE is mandatory to all the personnel involved in the care of patients[9]. PPE includes N95 face masks or surgical masks, protective eyewear such as goggles, medical gowns, and surgical gloves (sometimes double) for contact, and the use of the powered air-purifying respirators for all high-risk or aerosol-generating procedures. In daily medical practice, it is required to wear PPE for prolonged periods. At present, we are experiencing the pandemic caused by the SARS-CoV-2, whose disease was baptized by the World Health Organization with the name of COVID-19[10]. Due to its high contagion rate, the widespread use of protective measures, such as PPE, will, expectedly, rise the incidence of this headache.

There are only three studies that demonstrate the association of the use of PPE with headache, facial pain, and/or ear lobe discomfort. The prevalence of PPE-associated headache varies from 37 to 81%, with a frequency of > 6 episodes/month in 33%. About 81-88% reported the onset with < 60 min of use and 88% reported the end of the episode with equipment removal. The pain has been bilateral in all the patients; 87% reported as oppressive followed by 11.7% as throbbing quality, and its intensity was mild in 72%. Even when 83% reported a negative impact on their work performance, only 7% took a sick leave because of headache, and 31-59% required the use of abortive analgesics. It is important to take into account the presence of pre-existing headache, which was reported in 29-37%; among these patients, 91% reported an increase in the frequency and duration of episodes and poorer work performance. The two individual factors that increase the risk of developing PPE-associated headache are the existence of a previous headache, such as migraine and tension-type headache, and a longer period of usage, usually > 4 h/day[8,11,12].

In future, it will be indispensable to prepare specifics protocols for situations like these, since in addition to the protection of hospital staff, it is necessary to think of their comfort as well. There are two approaches that could be exploited: one is directed to the PPE, by inviting manufacturers to look for alternatives, either in materials or shapes that reduce the possibility of discomfort to their users (one example was a fighter pilot that suffered from ECH from his helmet; the successful treatment was the switching of the non-adjustable one-piece helmet to a two-piece adjustable helmet, this measure disappeared the headache)[13] and the second possible contribution would be to modify the infrastructure and policies of hospitals, shortening working periods, rotating periods in different hospital areas, where personnel can rest without the equipment and decrease the period of exposure.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethical disclosures

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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References

1. Lance JW. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache classification committee of the international headache society. Cephalalgia. 1988;8:1-96.
2. Headache classification committee of the international headache society (IHS) the international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38:1-211.
3. Krymchantowski AV. Headaches due to external compression. Curr Pain Headache. 2010;14:321-4.
4. Kao TW, Huang KC, Huang YL. The physiological impact of wearing an N95 mask during hemodialysis as a precaution against SARS in patients with end-stage renal disease. J Formos Med Assoc. 2004;103:624-8.
5. Hoiland RL, Tymko MM, Bain AR, Wildfong KW, Monteleone B, Ainslie PN. Carbon dioxide-mediated vasomotion of extra-cranial cerebral arteries in humans: a role for prostaglandins? J Physiol. 2016;12:3463-81.
6. Pestronk A, Pestronk S. Goggle migraine. *N Engl J Med*. 1983;*308*:226-7.
7. Krymchantowski A, Barbosa JS, Cvaigman M, Lorenzatto W, Silva MT. Helmet-related, external compression headache among police officers in Rio de Janeiro. Medgenmed. 2004;6:45.
8. Ong JJ, Bharatendu C, Goh Y, Tang JZ, Sooi KW, Tan YL, et al. Headaches associated with personal protective equipment-a cross-sectional study among frontline healthcare workers during COVID-19. Headache. 2020;60:864-77.
9. Andersen BM. Personal protective equipment. In: Prevention and Control of Infections in Hospitals: practice and Theory. Berlin, Germany: Springer; 2019. p. 1061-4.
10. Fernández-Garza, LE, Marfil A. Neurological aspects that should not be forgotten during the COVID-19 pandemic. Int J Med Health. 2020;3:1-3.
11. Rebmann T, Carrico R, Wang J. Physiologic and other effects and compliance with long-term respirator use among medical intensive care unit nurses. Am J Infect Control. 2013;41:1218-23.
12. Lim E, Seet R, Lee KH, Wilder-Smith E, Chuah B, Ong B. Headaches and the N95 face-mask amongst healthcare providers. Acta Neurol Scand. 2006;113:199-202.
13. Kharbanda GC, Ganjoo AR, Chadha WC. A strange case of headache in a fighter aircrew: a case study. Indian J Aerospace Med. 2008;52:20-5.

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ORIGINAL ARTICLE

Clinical characteristics and surgical management of spinal cord tumors in non-Caucasian Hispanic children

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Abstract

Objective: *Little literature exists about spinal cord tumors in Hispanic children.* **Methods:** *We conducted a retrospective review in 45 Mexican children presenting with spinal cord tumors between 1985 and 2015.* **Results:** *We observed a higher incidence of spinal cord tumors in males (62.22%). The mean age at diagnosis was 8.75 years. Tumors were more frequently observed among school-age children (42.22%). Motor deficit was the most common clinical manifestation (97.77%). Most tumors were intramedullary. Astrocytoma was the most frequent histological subtype. Laminotomy with laminoplasty was the main operative procedure performed in our study. Total resection of the tumors was achieved in 20% of the cases. Post-surgical complications were observed in 44% of the cases.* **Conclusions:** *Pediatric patients with spinal cord tumors can receive surgical management with an acceptable low surgical morbidity. The clinical phenotype observed in our population has certain similitudes with respect to what it is described in Caucasians.*

Key words: *Spinal cord. Spinal cord tumors. Intramedullary tumors. Extradural tumors.*

Características clínicas y manejo quirúrgico de tumores raquimedulares en niños hispanos

Resumen

Objetivo: *Existe poca literatura acerca de tumores raquimedulares en niños hispanos.* **Métodos:** *Realizamos una revisión retrospectiva de 45 niños mexicanos que presentaron tumores raquimedulares entre 1985 y 2015.* **Resultados:** *Observamos mayor incidencia de tumores raquimedulares en varones (62.22%). La edad promedio al momento del diagnóstico fue de 8.75 años. Los tumores fueron observados con mayor frecuencia en niños en edad escolar (42.22%). El déficit motor fue la manifestación clínica más frecuente (97.77%). La mayoría de los tumores fueron intramedulares. El astrocitoma fue el subtipo*

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histológico más común. La laminotomía con laminoplastía fue el procedimiento quirúrgico realizado con mayor frecuencia en nuestro estudio. La resección tumoral total se logro en 20% de los casos. Las complicaciones quirúrgicas ocurrieron en 44% de los pacientes. **Conclusiones:** *los pacientes pediátricos con tumores raquimedulares pueden recibir tratamiento quirúrgico con una baja morbilidad. El fenotipo clínico observado en nuestra población tiene ciertas similitudes respecto a lo descrito en caucásicos.*

Palabras clave: *Médula espinal. Tumores raquimedulares. Tumores intramedulares. Tumores extradurales.*

Introduction

Spinal cord tumors are rare in adults and occur at a considerably lower frequency in children. The proportion between spinal cord and intracranial tumors described in the pediatric population varies from 1:4.8 to 1:20, depending on the series reviewed[1]. Incidence of spinal cord tumors in high-income countries such as the United States is 1 case/100,000 children[2], mainly affecting scholars and adolescents[3,4]. These tumors can arise from the spinal cord or from the adjacent structures, and according to their location, they can be classified as intra- or extradural. Moreover, intradural tumors are divided into intramedullary and extramedullary[5].

The current literature describes that two-thirds of the total spinal cord neoplasia occurring in children are extradural. These include bone tumors, tumors of the epidural space, and extraspinal tumors that invade such space. On the other hand, 35% of the spinal cord tumors in pediatric patients are intramedullary, representing 4-6% of the total central nervous system neoplasia[6]. Astrocytoma, ganglioma, and ependymoma are the histological subtypes most frequently observed in the intramedullary location[2]. Such tumors often localize at cervical and thoracic levels of the spinal cord in almost 50% of the cases, being less frequently observed at lumbar segments[7,8]. Finally, intradural extramedullary neoplasia is rare and most of them are leptomeningeal metastasis from brain tumors[9].

Most of what it is currently known about epidemiology and clinical characteristics of spinal cord tumors in children comes from series in Caucasians. However, few studies have described the clinical behavior of these tumors in other populations. In developing countries like Mexico, there are only few reports of spinal cord tumor in children[10-12], some of which were published before the advent and availability of novel brain imaging tools currently used for the diagnostic and surgical approach of these neoplasia[10,11]. Therefore, it is of major relevance to have updated information about the frequency, clinical behavior, diagnostic tools, surgical strategies, and post-operative clinical outcomes of spinal cord tumors in our children population. Here, we report our experience in the management of spinal cord tumors by reviewing the clinical registries of children that attended and were regularly followed at the Department of Neurosurgery of the Pediatric Hospital of Mexico, a third-level National Reference Center in Mexico City. We believe that our clinical description contributes to the knowledge of spinal cord tumors in Hispanic children and provides valuable data for future studies aimed to compare the clinical behavior of spinal cord tumors among pediatrics with different ethnic backgrounds.

Methods

We conducted a retrospective review of the clinical and radiological database of the Pediatric Hospital of Mexico "Federico Gomez," looking for clinical cases of children with spinal cord tumors that attended and were regularly followed at our center during the period from 1985 to 2015. Demographic, clinical, and imaging data from participants were retrieved from the database of our hospital. The collected information included relevant neurological manifestations, anatomical location and histological subtype of the tumors, category of imaging tools used for the diagnosis, surgical approaches employed for tumor resection, and post-operative clinical outcomes. Descriptive statistics were used to clinically characterize the study population. Frequencies and proportions were calculated for categorical data. Means, medians, and standard deviations were used for continuous data. Calculations for descriptive statistics were performed using GraphPad Prism v5 (La Jolla, CA, USA). The study was approved by the Ethics Committee of our institution and was conducted with strict adherence to the Official Mexican Law NOM-012-SSA3-2012 that establishes the criteria for the execution of health research projects in humans.

Results

Participants' characteristics

A total of 45 children with spinal cord tumors were included in the study. Their mean age at diagnosis was

Table 1. Clinical characteristics of Hispanic children with spinal cord tumors

Variable	n = 45
Age at onset, mean (range)	8.75 (0.5-17)
Gender	
Male, n (%)	28 (62.22)
Female, n (%)	17 (37.77)
Male/female ratio	1.64:1
Age group	
Infants, n (%)	4 (8.88)
Pre-scholars, n (%)	9 (20)
School-age children, n (%)	19 (42.22)
Adolescents, n (%)	13 (28.88)
Clinical findings before surgical management	
Motor deficit, n (%)	44 (97.77)
Pain, n (%)	39 (86.66)
Pain referred to the corresponding dermatomes, n (%)	36 (80)
Radicular pain, n (%)	3 (6.66)
Hypoesthesia, n (%)	38 (84.44)
Dysesthesia, n (%)	25 (55.55)
Paresthesia, n (%)	13 (28.88)
Urinary incontinency, n (%)	29 (64.44)
Abnormal gait, n (%)	16 (35.55)
Fecal incontinence, n (%)	10 (22.22)
Scoliosis, n (%)	18 (40)
Kyphoscoliosis, n (%)	6 (13.33)
Falls, n (%)	6 (13.33)
Cervical stiffness, n (%)	6 (13.33)
Muscle contractures, n (%)	6 (13.33)
Hyperreflexia, n (%)	6 (13.33)
Clonus, n (%)	6 (13.33)
Atrophy of muscles of the hands, n (%)	6 (13.33)
Hydrocephalus, n (%)	4 (8.88)
Headache, n (%)	4 (8.88)
Seizures, n (%)	4 (8.88)

Table 2. Frequency and distribution of spinal cord tumors according to their anatomical location and histological subtype

Localization/ histological subtype	Frequency	% of tumors at specific localization	% from total
Intramedullary	20	--	44.44
Astrocytoma	14	70	31.11
Ependymomas	5	25	11.11
Ganglioma	1	5	2.22
Extradural	18	--	40
PNETs	6	33.33	13.33
Metastases	4	22.22	8.88
Sarcomas	3	16.66	6.66
Neuroblastoma	1	5.55	2.22
Lymphomas	1	5.55	2.22
Other not specified	3	16.66	6.66
Intradural extramedullary	7	--	15.55
Meningiomas	4	57.14	8.88
Ependymomas	1	14.28	2.22
Schwannomas	1	14.28	2.22
Dermoid cysts	1	14.28	2.22

PNETs: primary neuroectodermal tumors.

8.75 years (range 5 months-17 years). The most ancient case occurred 31 years before the conduction of the current study. From these, 28 patients were male (62.22%) and 17 female (37.77%), with a male/female ratio of 1.64:1. The age group with the highest incidence of spinal cord tumors was composed of school-age children with 19 cases (42.22%), followed by adolescents (13 cases, 28.88%), pre-scholars (9 cases, 20%), and infants (4 cases, 8.88%). All the patients were born in Mexico and their parents referred themselves as belonging to the Mexican Mestizo race. The clinical and demographic characteristics of participants are summarized in Table 1.

Tumors location and histological subtype

Intramedullary tumors were the most frequent lesions affecting our population, representing the 44.44% of the cases (20 patients) followed by extradural and intradural extramedullary tumors with 18 (40%) and 7 (15.55%) cases, respectively. In addition, six cases of intramedullary lesions were holocordal neoplasia (13.33%). All cases received histopathological diagnosis. Independently of the tumors' location, astrocytoma was the most frequent histological subtype, followed by primitive neuroectodermal tumors (PNETs), ependymoma, meningioma, and metastases. The frequency and anatomical localization of the different histological subtypes of spinal cord tumors observed in our series are shown in Table 2.

Neurological findings

The most common clinical findings observed in order of frequency were motor deficit (97.77%), pain (86.66%), urinary incontinence (64.44%), abnormal gait (35.55%), and fecal incontinence (22.22%) (Table 1). Furthermore, 53.33% of patients had alterations of the statics

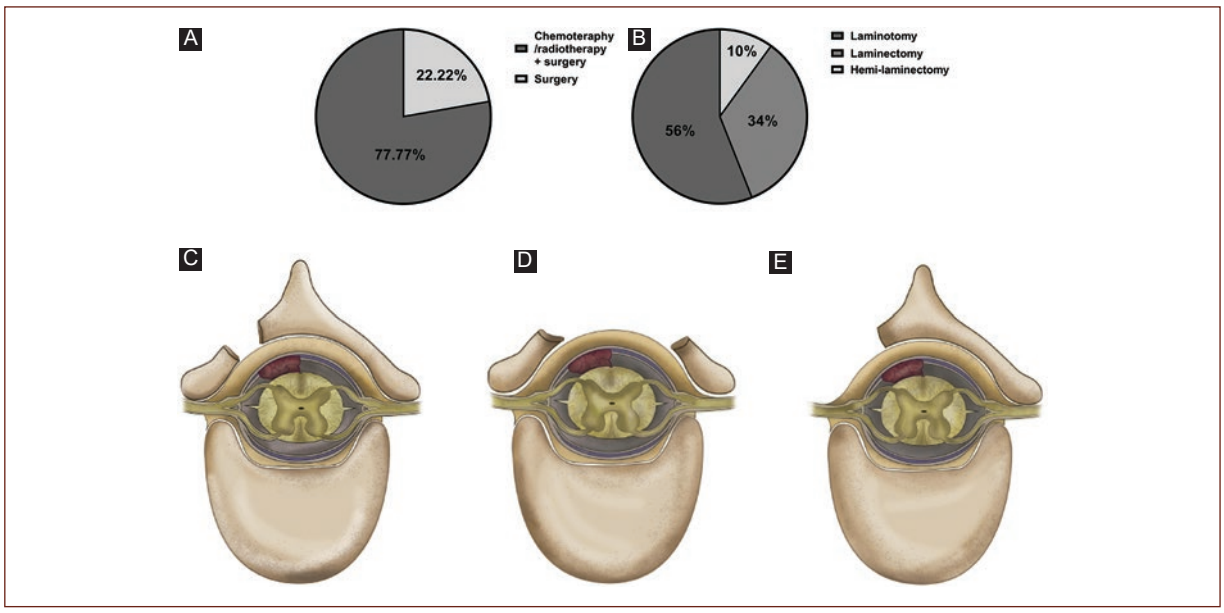

Figure 1. Treatment approaches for pediatric patients with spinal cord tumors. **A:** Treatment modalities for children with spinal cord tumors. **B:** Surgical procedures performed for the resection of spinal cord tumors. **C:** Representative figure of the operative field provided by posterior laminotomy. **D:** Laminectomy. **E:** Hemi-laminectomy.

of the spine; 18 cases presented scoliosis (40%) and 6 had kyphoscoliosis (13.33%).

Although motor deficit was the main neurological finding, this sign occurred as the first clinical manifestation only in 22 cases (48.88%). The mean time since the presentation of the motor deficit and surgery was 4.5 months. This deficit was observed in all cases of astrocytoma and intramedullary ependymoma. Other neurological findings observed in our series, especially among patients with cervical-thoracic holocordal tumors included falls, tabetic gait, cervical stiffness, deltoid, supraspinatus, biceps and triceps muscle contractures, as well as hyperreflexia, clonus, and atrophy of intrinsic muscles of the hands.

Regarding pain, this was referred along the dermatomes corresponding to the anatomical location of the tumors in 80% of patients. This symptom was most common in patients with extradural tumors. Three patients had radicular pain (6.66%). Among children affected by cervical tumors, we observed neck pain that was exacerbated with inclination of the head to the contralateral side of the lesion. Sensory deficits manifested as hypoesthesia in 38 cases, dysesthesia in 25 patients, and paresthesia in 13 cases. These sensory alterations always occurred in the dermatomes corresponding to the location of the tumors. Urinary and fecal incontinency occurred in patients with neoplasia of the lumbosacral region or holocordal tumors. Hydrocephalus was detected in 4 cases (8.88%) and was accompanied by headache and seizures secondary to intracranial hypertension. Neurological features observed in our population are summarized in Table 1.

Diagnostic approach

From the 45 patients included in the current study, only 13 presented images of brain computerized axial tomography (computed tomography [CT]) scan and magnetic resonance imaging (MRI) at their first medical appointment. Overall, 36 patients underwent to CT scan (80%), 38 to MRI (84.44%), 27 to electromyography (60%), and 31 to evoked potentials (68.88%). In 29 cases, urodynamic studies were performed (64.44%) including 18 cases with intramedullary tumors. Furthermore, anorectal manometry was performed in 19 patients (42.22%), 11 of them with intramedullary lesions.

Surgical management

Overall, 10 patients were subjected to surgery as their only management strategy, whereas the rest received multidisciplinary oncological management, which included surgery, radiotherapy, and chemotherapy (Fig. 1A). A total of 50 surgical procedures were performed in the 45 cases included in the study (Table 3 and Fig. 1B). Laminotomy was the most

frequent operative procedure used for the treatment of 28 cases (56%, n = 50) (Fig. 1C). From these, 17 were laminotomies followed by laminoplasty as previously described[13,14]. Furthermore, 17 laminectomies (34%) and 5 hemi-laminectomies (10%) were performed (Fig. 1D and E). In all cases, a posterior spinal approach was used. For the resection of intramedullary tumors, a classic myelotomy through microsurgical dissection was performed. Ultrasonic cavitation was used only for three cases. The interval from symptoms onset to surgery was lower than 1 month in 3 cases (6.66%), 1-6 months in 36 cases (80%), 7-12 months in 2 cases (4.44%), and higher than 12 months in 4 patients (8.88%), with an overall mean of 9.5 ± 8.5 months (Table 3).

Table 3. Surgical management and post-operative outcomes in children with spinal cord tumors

Management modality	n = 45
Radiotherapy + chemotherapy + surgery, n (%)	35 (77.77)
Only surgical resection, n (%)	10 (22.22)
Interval from onset to surgery, mean (SD)	9.5 (8.5)
< 1 month, n (%)	3 (6.66)
1-6 months, n (%)	36 (80)
7-12 months, n (%)	2 (4.44)
> 12 months, n (%)	4 (8.88)
Surgical procedure	n = 50
Laminotomy, n (%)	28 (56)
Laminotomy + laminoplasty, n (%)	17 (34)
Laminectomy, n (%)	17 (34)
Hemilaminectomy, n (%)	5 (10)
Surgical outcome	n = 45
Complete tumor resection, n (%)	9 (20)
Subtotal tumor resection, n (%)	36 (80)
Post-operative complications	
CSF fistula, n (%)	9 (20)
Post-surgical motor deficit, n (%)	6 (13.33)
New-onset urinary incontinency, n (%)	3 (6.66)
Scoliosis, n (%)	1 (2.22)
Hemorrhage, n (%)	1 (2.22)

CSF: cerebrospinal fluid; SD: standard deviation.

Post-operative clinical outcomes

A complete tumor resection, defined by negative margins after histopathological analysis, was achieved in 9 cases (20%; Table 3). From these, five cases were cervical-thoracic astrocytoma, one cervical ependymoma, one cervical PNET, and two thoracic meningioma. All these cases remained without neurological deficits and their mean survival time from onset to the last known follow-up was 10 ± 4.5 years. Thirty-six cases had a subtotal tumor resection, from which 19 (52.77%) had a favorable outcome with no aggravation of the neurological deficit nor recurrence of the tumor after a mean follow up time of 4.5 ± 2.02 years. The recurrence status was confirmed on the basis of clinical and imaging findings during the outpatient follow-up period.

The most frequent complications observed after surgery were cerebrospinal fluid fistulas in 9 cases (20%), post-surgical motor deficit in 6 cases (13.33%), new-onset urinary incontinence in 3 cases (6.66%), hemorrhage in 1 case (2.22%), and scoliosis in 1 case (2.22%). Finally, 3 dysfunctions (8.88%) occurred during the period evaluated in the current study and were caused by two anaplastic astrocytoma and one rhabdomyosarcoma.

Discussion

In the current study, we provide the first clinical description of the full spectrum of tumors affecting the spine and spinal cord in Mexican children[11,12]. Hence, our data may constitute relevant evidence useful for the diagnostic approach and management of spinal cord tumors in non-Caucasian Hispanic pediatric patients from Latin American populations. Based on epidemiological studies conducted at developed countries[2], the incidence of pediatric spinal cord tumors in Mexico is expected to be high, considering that children have constituted a major proportion of the general population in our country during the period of time comprehended in this study. Nonetheless, only 226 cases occurring in our country, including the 45 children described here, have been formally reported in literature during the past 3 decades[11,12]. This suggests a high degree of underdiagnosis and subreport. Despite this, our work and previous local studies show certain similitudes and discrepancies in the clinical phenotype of Mexican Hispanic children with spinal cord tumors with respect to what is described in Caucasian series (Table 4). First, we observed a higher incidence of these tumors in male, and a predominant affection to scholars and adolescents, which have been also reported by other

Table 4. Clinical characteristics of spinal cord tumors in children from different regions

Race/origin	Age at onset (years), mean	Predominant gender	Mortality (%)	Tumor localization	Histological subtype	Reference
Hispanic	8.75	Male	8.88	Intramedullary	Astrocytoma	Current study
Hispanic	--	Male	--	Intradural extramedullary	Dermoid cyst	11
Hispanic	5.2	Male	21.7	--	Primary neuroectodermal tumors	12
Caucasian	6.6	Male	--	Intramedullary	Dermoid tumors, epidermoid tumors, and teratomas	15
Caucasian	8.5	Male	11.9	Intramedullary	Low-grade glioma	16

researchers[2,10-12,15,16]. Second, considering the experience of our department in the management of brain neoplasms in children (810 cases in 36 years)[17], the ratio between spinal cord tumors and intracranial neoplasia derived from the present work (45 cases in 31 years) is 1:15.5 and 1:17.6 if we compare our series with the 511 brain tumors observed during 20 years in the Spanish Hospital of Mexico[18]. These data coincide with the ratio observed in other studies in Caucasians[1]; however, this information may not be accurate due to the possible local degree of underdiagnosis mentioned above.

On the other hand, we observed a higher incidence of intramedullary lesions followed by those of extradural location in our population. In this regard, there is no consensus about the anatomical area most predominantly affected by these tumors since some studies show a higher frequency of extradural lesions[16,19,20], while others describe a higher incidence of intramedullary tumors[15,21-26]. It is probable that factors specific to each population explain these discrepancies. Our data also confirm the previous descriptions about the most common histological type of spinal cord tumors observed in children[2,9], as astrocytoma was the most incident tumor in our series regardless of their location. Furthermore, a remarkable finding derived from this work is the high frequency of extradural PNET type neoplasms occurring in our patients, which has been also reported in other Mexican series[12]. These tumors are conformed by undifferentiated cells, with varying degrees of pleomorphism and a slight tendency to acquire neuroectodermal characteristics[27]. Their incidence is extremely low, and some studies show that they represent less than 1% of all neoplasms that affect the spinal cord[28]. The average age at which they have been previously diagnosed is 24 years and their exact epidemiology in children remains unknown[29]. Thus, our data suggest that the incidence of spinal cord PNET in the pediatric population may be higher than previously thought.

The identification of spinal cord tumors in children is a major diagnostic challenge due to their rarity and unspecific clinical features. In this regard, our data, as well as previous reports[30], show that a high proportion of pediatric patients with spinal cord tumors present motor deficits as their initial manifestation. Furthermore, our findings suggest that the presence of pain distributed along with a dermatome, radicular pain, hypoesthesia, paresthesia, dysesthesia, urinary and fecal incontinence, as well as gait disorders in a child otherwise healthy, should suggest the presence of a spinal cord tumor. Regarding surgical management of these lesions, we found that laminotomy by posterior approach is a safe and not deforming procedure, as previously reported[13,14]. Interestingly, we also observed that laminectomy caused kyphosis in only 1 of 17 patients subjected to such procedure at least until the last known follow-up, which represents a lower frequency than reported by other researchers who described that two-thirds of the subjects undergoing laminectomy developed deformity of the spine[31], especially when laxity of supporting tissues was induced by the adjuvant oncological treatment[32]. Moreover, the occurrence of post-surgical complications in our study was low regardless of the operative approach, and fatal cases were not directly associated with the surgical resection of the tumors. Thus, our data show that pediatric patients with spinal cord tumors can receive surgical management with an acceptable low surgical morbidity.

Our study possesses all the limitations of a retrospective design in relation to the access and collection of the clinical information. In fact, we could not address the prognostic value of clinical variables and treatment approaches as most of the patients were not further followed after they reach the adulthood. Thus, our survival estimations only represent those patients that remain alive at the last known follow-up. In addition, we did not find objective quantitative evaluations of the post-operative neurological status of the patients within their clinical registries. Such information would have informed us about the effect of the surgical treatment on the neurological functionality. Finally, the fact that the current study was conducted at a single third-level medical center made us unable to perform a population-based comparison, which limited our ability to estimate the local incidence of spinal cord tumors in children and may restrict the representativeness of our data.

Conclusions

Pediatric patients with spinal cord tumors can receive surgical management with an acceptable low surgical morbidity. The clinical phenotype observed in our population has certain similitudes concerning what it is described in caucasians. This study provides a valuable clinical description of spinal cord tumors that can help in future research in non-caucasian Hispanic children.

Conflicts of interest

The authors declare that they do not have any conflicts of interest to report.

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Ethical responsibilities

Protection of people and animals. The authors declare that the procedures followed in the current study were performed in agreement to the ethical standards of the responsible human experimentation committee, the World Medical Association, and the Declaration of Helsinki.

Confidentiality of the 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 have obtained the informed consent of the patients and/or subjects referred to in the article. This document is held by the correspondence author.

References

1. Di Lorenzo N, Giuffre R, Fortuna A. Primary spinal neoplasms in childhood: analysis of 1234 published cases (including 56 personal cases) by pathology, sex, age and site. Differences from the situation in adults. Neurochirurgia (Stuttg). 1982;25:153-64.
2. Constantini S, Epstein FJ. Intraspinal tumors in infants and children. In: Youmans J, editor, Neurological Surgery. 4th ed, Vol. 4. Philadelphia (PA): WB Saundersp; 1996. p. 3123-33.
3. Schellinger KA, Propp JM, Villano JL, McCarthy BJ. Descriptive epidemiology of primary spinal cord tumors. J Neurooncol. 2008;87:173-9.
4. Duong LM, McCarthy BJ, McLendon RE, Dolecek TA, Kruchko C, Douglas LL, et al. Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004-2007. Cancer. 2012;118:4220-7.
5. Van Goethem JW, van den Hauwe L, Ozsarlak O, De Schepper AM, Parizel PM. Spinal tumors. Eur J Radiol. 2004;50:159-76.
6. DeSousa AL, Kalsbeck JE, Mealey J Jr., Campbell RL, Hockey A. Intraspinal tumors in children. A review of 81 cases. J Neurosurg. 1979;51:437-45.
7. Epstein F, Ragheb J. Intramedullary tumors of the spinal cord. In: Cheek W, editor. Pediatric Neurosurgery: Surgery of the Developing Nervous System. Philadelphia (PA): WB Saunders; 1994. p. 446-57.
8. Brotchi J, Noterman J, Baleriaux D. Surgery of intramedullary spinal cord tumours. Acta Neurochir (Wien). 1992;116:176-8.
9. Rossi A, Gandolfo C, Morana G, Tortori-Donati P. Tumors of the spine in children. Neuroimaging Clin N Am. 2007;17:17-35.
10. Rueda Franco F, Monson de Souza MB, Takenaga Mesquida R. Intraspinal tumors in children. Review of 24 cases. Bol Med Hosp Infant Mex. 1975;32:1073-94.
11. Rueda-Franco F. Tumores intraspinales en niños. Revisión de 130 enfermos. Cir Cir. 1990;57:143-52.
12. González-Sosa E, Anaya-Jara M, Marhx-Bracho A, Rueda-Franco F. Neoplasias espinales extradurales. Experiencia de 15 años en el Instituto Nacional de Pediatría. Acta Pediatr Mex. 2009;30:216-9.
13. Raimondi AJ, Gutierrez FA, Di Rocco C. Laminotomy and total reconstruction of the posterior spinal arch for spinal canal surgery in childhood. J Neurosurg. 1976;45:555-60.
14. Rama B, Markakis E, Kolenda H, Jansen J. Reconstruction instead of resection: laminotomy and laminoplasty. Neurochirurgia (Stuttg). 1990;33 Suppl 1:36-9.
15. Wilson PE, Oleszek JL, Clayton GH. Pediatric spinal cord tumors and masses. J Spinal Cord Med. 2007;30 Suppl 1:S15-20.
16. Spacca B, Giordano F, Donati P, Genitori L. Spinal tumors in children: long-term retrospective evaluation of a series of 134 cases treated in a single unit of pediatric neurosurgery. Spine J. 2015;15:1949-55.
17. Chico-Ponce de León F, Castro-Sierra E, Perezpeña-Diazconti M, Gordillo–Domínguez LF, Santana–Montero BL, Rocha–Rivero LE, et al. Tumores intracraneanos del niño. Bol Med Hosp Inf Mex. 2006;63:367-81.
18. Anaya-Delgadillo G, de Juambelz-Cisneros PP, Fernández-Alvarado B, Pazos-Gómez F, Velasco-Torre A, Revuelta-Gutiérrez R. Prevalence of central nervous system tumours and histological identification in the operated patient: 20 years of experience. Cir Cir. 2016;84:447-53.
19. Kanos CC, Muhlbauer MS. Extramedullary, intradural and extradural spinal cord tumors. In: McLone DG, editor. Pediatric Neurosurgery. 4th ed. Philadelphia (PA): WB Saunders Company; 2001. p. 873-84.
20. Wetjen NM, Raffel C. Spinal extradural neoplasms and intradural extramedullary neoplasms. In: Albright AL, Pollack IF, Adelson PD, editor. Principles and Practice of Pediatric Neurosurgery. New York: Thieme; 2008. p. 694-705.
21. Nadkarni TD, Rekate HL. Pediatric intramedullary spinal cord tumors. Critical review of the literature. Childs Nerv Syst. 1999;15:17-28.
22. Albright AL. Pediatric intramedullary spinal cord tumors. Childs Nerv Syst. 1999;15:436-8.
23. Jallo GI, Freed D, Epstein F. Intramedullary spinal cord tumors in children. Childs Nerv Syst. 2003;19:641-9.
24. Townsend N, Handler M, Fleitz J, Foreman N. Intramedullary spinal cord astrocytomas in children. Pediatr Blood Cancer. 2004;43:629-32.
25. Kumar R, Singh V. Intramedullary mass lesion of the spinal cord in children of a developing milieu. Pediatr Neurosurg. 2004;40:16-22.
26. Auguste KI, Gupta N. Pediatric intramedullary spinal cord tumors. Neurosurg Clin N Am. 2006;17:51-61.

27. Dehner LP. Primitive neuroectodermal tumor and Ewing's sarcoma. Am J Surg Pathol. 1993;17:1-3.
28. Ellis JA, Rothrock RJ, Moise G, McCormick PC 2nd, Tanji K, Canoll P, et al. Primitive neuroectodermal tumors of the spine: a comprehensive review with illustrative clinical cases. Neurosurg Focus. 2011;30:E1.
29. Engelhard HH, Villano JL, Porter KR, Stewart AK, Barua M, Barker FG, et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equina. J Neurosurg Spine. 2010;13:67-77.
30. Epstein F, Epstein N. Surgical management of holocord intramedullary spinal cord astrocytomas in children. J Neurosurg. 1981;54:829-32.
31. Jallo GI, Kothbauer KF, Epstein FJ. Intrinsic spinal cord tumor resection. Neurosurgery. 2001;49:1124-8.
32. Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg. 2000;93:183-93.

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ORIGINAL ARTICLE

Factors influencing locomotor capacity of hemiparetic post-stroke patients

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Abstract

Background: *The locomotor recovery is the most desired goal by patients and clinicians. Measurement of gait speed (GS) provides a fast and reliable clinical parameter for this function. The aim of this study was to verify the relationship between GS and different variables, such as age, injury time, body composition, functional mobility, spasticity, motor recovery, and muscle strength.* **Material and methods:** *The study included 24 patients with average age 57.6 (± 10.5) years post-stroke hemiparetics. Two groups of patients were formed, those who walked with GS higher than 0.80 m/s (n = 8) and another group with GS lower than 0.80 m/s (n = 16). They were evaluated by the GS test, Timed Up and Go Test (TUGT), Fugl-Meyer scale (FMS), Modified Ashworth Scale (MAS), bilateral dynamometry of extensors and flexors knee, and determination of body mass index (BMI).* **Results:** *In the correlation analysis between GS and other variables, in the group with GS higher than 0.80 m/s, there was a significant correlation with TUGT (r = –0.77) and strength tests (r ≥ 0.80). In the group with GS <0.80 m/s, there was a moderate to strong correlation with TUGT (r = –0.87), FMS (r = 0.74), MAS (r = –0.62), and quadriceps femoris muscle strength in paretic side (r = 0.55). In both groups, no significant correlations were found with age, stroke time, and BMI.* **Conclusion:** *The study indicates that the combination of an important motor deficit expressed by greater strength asymmetry between the paretic and non-paretic sides, and a greater degree of spasticity results in worse performance in the GS.*

Key words: *Gait. Hemiparesis. Stroke.*

Factores que influyen en la capacidad locomotora de los pacientes hemiparéticos por accidente cerebrovascular

Resumen

Antecedentes: *La recuperación locomotora es el objetivo más deseado por los pacientes y los clínicos. La medición de la velocidad de la marcha (VM) proporciona un parámetro clínico rápido y fiable para esta función. El objetivo de este estudio fue verificar la relación entre VM y diferentes variables, como la edad, el tiempo de lesión, la composición corporal, la mo-*

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vilidad funcional, la espasticidad, la recuperación motora y la fuerza muscular. **Material y métodos:** *El estudio incluyó a 24 pacientes con una edad promedio de 57.6 (± 10.5) años después de un accidente cerebrovascular. Se formaron dos grupos de pacientes, los que caminaron con VM superior a 0.80 m/s (n = 8), y otro grupo con VM inferior a 0.80 m/s (n = 16). Fueron evaluados por la prueba de VM, la prueba Timed Up and Go (TUG), la escala de Fugl-Meyer (EFM), la escala de Ashworth modificada (EAM), la dinamometría bilateral de extensores y flexores de rodilla, y la determinación del índice de masa corporal (IMC).* **Resultados:** *En el análisis de correlación entre la VM y otras variables, en el grupo con VM superior a 0.80 m/s hubo una correlación significativa con la prueba TUG (r = –0.77) y la pruebas de fuerza (r ≥ 0.80). En el grupo con VM inferior a 0.80 m/s hubo una correlación de moderada a fuerte con la prueba TUG (r = –0.87), la EFM (r: 0.74), la EAM (r = –0.62) y la fuerza muscular del cuádriceps femoral en el lado parético (r = 0.55). En ambos grupos no se encontraron correlaciones significativas con la edad, el tiempo desde el accidente cerebrovascular y el IMC.* **Conclusión:** *El estudio indica que la combinación de un importante déficit motor, expresado por una mayor asimetría de fuerza entre los lados parético y no parético, y un mayor grado de espasticidad resulta en un peor desempeño en la VM.*

Palabras clave: *Marcha. Hemiparesia. Accidente cerebrovascular.*

Introduction

Stroke is one of the main causes of hospitalizations and mortality in Brazil and worldwide. In general, it causes some kind of deficiency, either partial or complete[1]. The motor deficits resulting from this disease cause muscle weakness, reduced mobility, and limited ability to perform functional tasks and affect about 40% of people who do not walk independently in the community[2].

It is understood that the non-paretic lower limb has a higher proportion of body weight that results in the oscillation of the orthostatic posture, characterizing an asymmetrical profile in weight transfer and greater oscillations on the paretic side than the non-paretic side, hindering the ability to walk. These changes in gait cause postural instability, limit gait capacity, increasing the risk of falls, and compromising the functional independence of these patients[3].

Recovery from walking is the most desired goal for patients and clinicians. For Fritz and Lusardi[4], gait speed (GS) is the "sixth vital sign." As a basic clinical parameter, this function is evaluated by the GS test (GST), which is easy to apply, fast, and reliable. In general, the patients with the best performance in GS (>0.80 m/s) are those who present with the lowest deficits, the best functional performance, and greater independence in the activities of daily living (ADLs), being usually independent ambulators in the community. On the other hand, those with poorer performance in GS (<0.80 m/s) are the most neurologically compromised patients, who present higher functional dependence, higher risk of falls, and hospitalization, and, in general, are home ambulators, especially those with GS < 0.40 m/s[5,6].

The aim of this research was to verify the relationship between GS and different variables, such as age, injury time, body composition, muscle strength, spasticity, and functional mobility in hemiparetic stroke patients.

Methodology

The study was descriptive correlational[7]. It was performed at the Center for Neurorehabilitation at Guilherme Guimbala College, in Joinville, Santa Catarina, Brazil. This study was approved by the Ethics Committee for Research Involving Human Beings (number 1.671.505). The participants were informed about the objectives and procedures of the study and signed the free and informed consent form.

Study participants

Consecutive volunteers of both genders aged 35 years and older, with a clinically stable history of stroke, in the subacute (between 3 and 6 months after the event) or chronic phases (more of 6 months after stroke episode) participated in the study. The patients were informed about the evaluation procedures that would be performed in the application of the study and were then invited to participate in the study.

As requisites for participation in the study, the inclusion and exclusion criteria described below were established.

Inclusion criteria

Hemiparetic stroke patients, clinically stable and in the subacute or chronic phases; age range from 35 years; be in agreement and show interest in participating in the project from start to finish; and then, they signed the free and informed consent form.

Exclusion criteria

Patients with hemiparesis due to other pathologies than stroke as well as hemiplegic patients; severe visual and/or auditory impairment; non-cooperative patients and/or patients with severe cognitive deficit assessed by means of the Mini-Mental State Examination with the cutoff points proposed by Bertolucci et al.[8]; and patients who could not walk independently, even if using walking aid devices such as crutch, cane, or walker were excluded from the study.

Measuring instruments and procedures

Registration form

This form included patient identification data and other general information (name, date of birth, address, telephone number, laterality, use of orthoses, and/or walking aids), sociodemographic data (gender, marital status, ethnicity, level of education, professional status, and profession), as well as clinical information (if the patient had more than one stroke, stroke type and time, main complaint, medications in use, adjuvant treatments, dysfunctions and/or associated pathologies, smoking, alcohol consumption, and family history of the disease) and anthropometric information (height, body mass, and body mass index [BMI]).

Digital Anthropometric Scale and Stadiometer

To measure body mass, a digital Omron® scale, model HBF-514C, BR, duly calibrated, was used, and the unit of measurement was recorded in kilograms (kg). Height was measured by means of a Sanny® stadiometer, model ES2020, manufactured by American Medical do Brasil Ltda., BR. This instrument has an accuracy of 0.1 mL, and the measurement was recorded in meters (m).

The BMI was obtained by means of the ratio between body mass (kg) and height (m) squared. The classification was performed according to the following cutoff points proposed by the World Health Organization (WHO): low weight (<18.50 kg/m²); normal weight (18.50-24.99 kg/m²); overweight (25.00-29.99 kg/m²); Grade I obesity (30.00-34.99 kg/m²); Grade II obesity (35.00-39.99 kg/m²); and Grade III obesity (≥40.0 kg/m²)[9].

Fugl-Meyer Scale (FMS)

The FMS was used to measure the level of motor impairment. It is noteworthy that in the present study only, the section destined to the motor evaluation of the lower limb was used, which includes the analysis of reflex activity, synergic muscle action in flexion and extension, and the movements with and without synergy. The patients were classified according to the degree of motor impairment in severe (0-7), strong (>7-14), moderate (>14-21), and light (>21-28)[10].

Modified Ashworth Scale (MAS)

The MAS was used to evaluate the degree of spasticity. It should be noted that only the spasticity of the quadriceps femoris muscle was evaluated.

This scale grades the spasticity in six levels: 0 – there is no increase in muscle tone; 1 – slight increase in muscle tone, manifested by a slight capture and release, or by minimal resistance at the end of the range of motion, when the affected part is moved in flexion or extension; 2 – slight increase in muscle tone, manifested by a slight capture followed by minimal resistance throughout the rest (less than half) of the range of motion; 3 – more accentuated increase in muscle tone during most of the range of motion, but the affected parts are easily moved; 4 – considerable muscle tone increased, difficult passive movement; and 5 – rigid affected parts, in flexion or extension[11].

Timed Up and Go Test (TUGT)

The TUGT was used to evaluate functional mobility[12,13]. The test requires the individual to stand up from a standardized chair with support, walk 3 m in a straight line on the floor, return to the chair, sitting in the initial position, and the time to perform this task is recorded in seconds. In addition to being a quick and easy to apply test, it has been widely used in individuals with stroke[14-17], as it has proven to be a valid and highly reliable instrument in the evaluation of this population.

At present, the TUGT is considered the best predictor of participation of individuals with stroke in the ADLs[18]. The instrument demonstrates good intraexaminer (ICC 0.95) and interexaminer reliability (ICC 0.98)[19].

GST

GS is considered a fast, practical, and reliable measure. It is related to functional mobility, level of independence, risk of falls, and hospitalization[4,6].

The patients were divided into two groups. The first group had the best performance in GST (>0.80 m/s). In

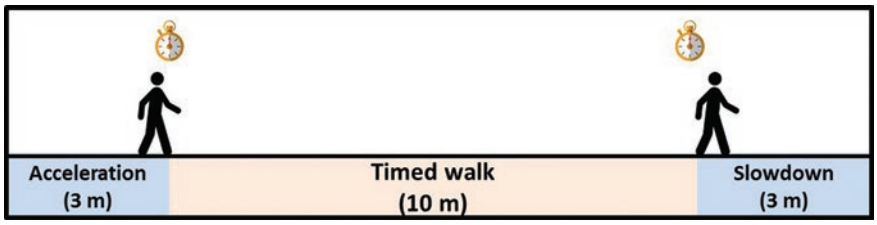

Figure 1. Method used for the gait speed test (*adapted of Fritz e Lusardi*[4]).

general, these patients are community ambulators and are less neurologically compromised. The second group, with the worst performance in GST (<0.80 m/s), is patients who present greater neurological impairment, present worse functional performance, risk of falls, and hospitalization, and, in general, are home walkers[4,6].

During the GST, the patients were instructed to perform the test as soon as possible on a 10 m path for timing (Fig. 1). To eliminate the effects of acceleration and deceleration in the test, a distance of 3 m was added at the beginning and end of the route. The patient started walking and, after a distance of 3 m, the stopwatch was activated. The time count ended at the 10 m marker, leaving another 3 m left for the patient's deceleration. Therefore, the unit of measurement used for GS was meters per second (m/s).

Dynamometry

To measure the strength of the extensor (EM) and flexor muscles (FM) knee, a Bonnet chair was prepared and adapted with a load cell, which is attached to the chair, allowing bilateral evaluation of the strength of the muscle groups mentioned above. A load cell of the IWM® brand, model GL-100 China, was used, which acts through the compression mechanism, with a capacity of 60 kg, properly calibrated. This cell has a division of 0.1 kg and sensitivity of 2.0 mV/V. Its excitation voltage is from 6 to 10 V.

The positioning of the patient and the equipment was different for each muscle group. For EM, the following positioning was adopted: patient seated in the chair, with the trunk supported on the backrest, with legs hanging, hip at 110° flexion in relation to the trunk and knees flexed at 90°[20-23]; for this muscle group, the equipment (sensor with the load cell) was positioned at the level of the distal third of the leg (just above the malleolar region), on the anterior face. For FM, it was used: patient seated in the chair, with the trunk supported on the backrest, hip at 110° flexion in relation to the trunk and knees flexed at 60°[24]; for this muscle group, the equipment was also positioned at the level of the distal third of the leg, however, on the posterior face. Figure 2 illustrates the positioning of the patient and the sensor with the load cell during the procedures.

Three bilateral measurements of each muscle group were performed in maximum voluntary isometric contraction during a period of 5 s[21,25], with an interval of 60 s between each measurement. It is noteworthy that the measurements were taken on alternate days and, as a reference, the arithmetic mean resulting from the three evaluations was recorded. The patient was instructed to perform as much force as possible from a green signal projected on the screen, which indicated the beginning of the test, and this strength should be maintained until the disappearance of the green color, indicating the end of the test.

Data analysis

Data tabulation and analysis were performed using GraphPad Prism 6® software, determining minimum, maximum, mean, and standard deviation values. To verify the relationship between the study variables (GS vs. other variables), we used Pearson's correlation test for parametric variables (BMI, TUGT, and muscle strength measurements through dynamometry) and Spearman's correlation test for non-parametric data (FMS and MAS). The significance level of 95% ($p < 0.05$) was considered.

Results

Twenty-four patients participated in the study, 12 men and 12 women with post-stroke hemiparesis. All patients suffered an ischemic stroke confirmed by examination of images such as computed tomography and/or magnetic resonance imaging. Two groups of patients were formed, those who walked with GS higher than 0.80 m/s and another with GS lower than 0.80 m/s.

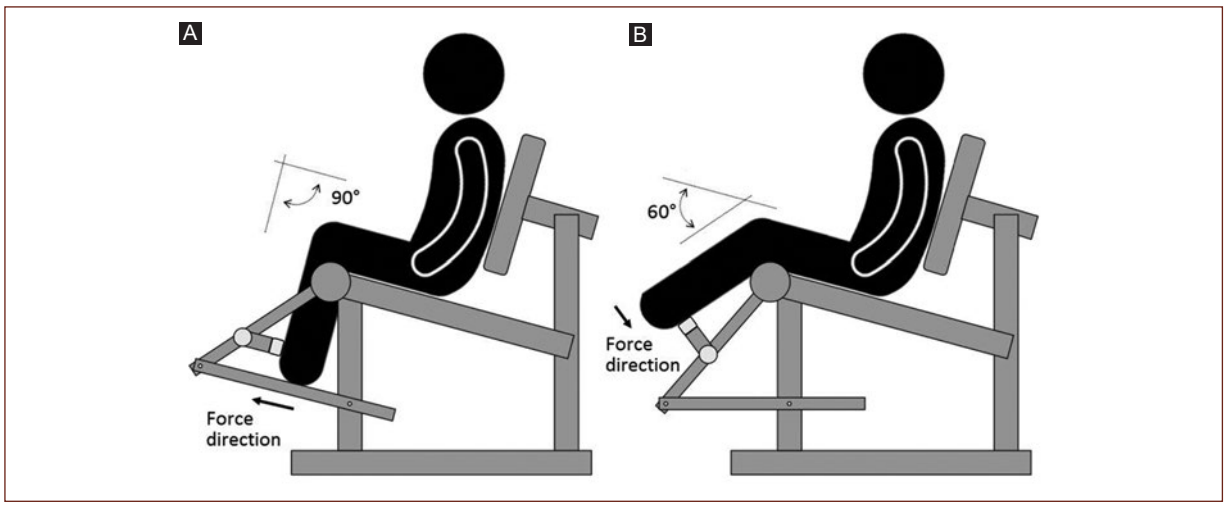

Figure 2. Positioning of the patient and the load cell for the evaluation of the muscle groups addressed in the study. **A:** extensors muscles dynamometry. **B:** flexors muscles dynamometry.

Table 1. Descriptive statistics of the group with good performance in gait speed test (> 0.80 m/s)

	Age	ST	BMI	TUGT	GST	FMS	MAS	ESp	ESnp	FSp	FSnp
M	59.3	23.3	27.4	12.7	1.06	25.6	0.50	17.6	24.0	7.9	12.0
DP	10.3	35.7	5.68	2.71	0.27	3.0	0.76	10.2	7.9	5.9	6.4
Minimum	46.0	4.00	17.6	8.62	0.80	19.0	0.0	7.30	13.3	2.8	5.4
Maximum	70.0	108	37.7	18.4	1.64	28.0	2.00	35.3	36.2	18.3	23.9

ST: stroke time (months); BMI: body mass index (kg/m^2), TUGT: timed up and go test (time in s); GST: gait speed test in 10 m (m/s); FMS: Fugl-Meyer scale – lower limb section (0-28); MAS: Modified Ashworth Scale (0-5); ESp: extensors muscle strength paretic side (kgf); ESnp: extensors muscle strength non-paretic side (kgf); FSp: flexors muscle strength paretic side (kgf); FSnp: flexors muscle strength non-paretic side (kgf).

Patients are seen at a physical therapy service twice a week regularly.

Next, data from the statistical analysis of the group with the best performance in GST (> 0.80 m/s) are presented. Tables 1 and 2 show descriptive statistics and correlation analysis data. Eight patients participated in this group, five men and three women.

Then, data from the statistical analysis of patients who wander with GST < 0.80 m/s (16 patients, 7 men and 9 women) are presented. Tables 3 and 4 present the descriptive statistics and correlation analysis data.

The groups when stratified based on GST were not different in terms of epidemiological and general clinical aspects, such as age, post-stroke injury time, and BMI. However, when compared to the other variables between the groups such as GST, TUGT, FMS, and MAS, it is observed that there is a significant difference between them. As for muscle strength tests, no significant difference was observed, although on the paretic side, the group with the worst performance in GS tests had a deficit of 28.4% in extensors muscles and 38.0% in flexors muscles lower than the group with the best performance. This may have an important clinical repercussion, as indicated in correlation tests involving this variable.

Discussion

Walking in hemiparetic patients after stroke is described as uncoordinated, arrhythmic, and unbalanced[5,26,27]. The GS is a clinical and biomechanical parameter that quickly, easily, and reliably translates performance in this primary function. In fact, there is a relationship between the performance in GST and the level of functional independence, risk of falls, and hospitalization of these patients[5,6].

In individuals affected by stroke, although GS is a determining factor of functional capacity, other variables may be associated with functional deficit, such as anthropometric characteristics[28]. In our study, the correlation between BMI and GS was weak and not significant for both groups. Similar results were found

Table 2. Correlation analysis of the group with good performance (gait speed test > 0.80 m/s)

	Age	ST	BMI	TUGT	FMS	MAS	ESp	ESnp	FSp	FSnp
r	0.66	–0.37	0.15	–0.77	0.70	–0.54	0.87	0.80	0.85	0.85
p	0.077	0.370	0.718	0.026	0.061	0.060	0.005	0.018	0.007	0.008

ST: Stroke time (months); BMI: body mass index (kg/m^2); TUGT: timed up and go test (time in s); FMS: Fugl-Meyer scale – lower limb section (0-28); MAS: Modified Ashworth Scale (0-5); ESp: Extensors muscle strength paretic side (kgf); ESnp: Extensors muscle strength non-paretic side (kgf); FSp: flexors muscle strength paretic side (kgf); FSnp: flexors muscle strength non-paretic side (kgf).

Table 3. Descriptive statistics of the group with worst performance (gait speed test < 0.80 m/s)

	Age	ST	BMI	TUGT	GST	FMS	MAS	ESp	ESnp	FSp	FSnp
M	56.8	20.1	28.9	35.1	0.38	19.5	1.9	12.6	23.3	4.9	11.7
DP	10.8	22.5	8.34	20.7	0.2	4.9	1.7	7.3	8.0	3.0	4.6
Minimum	37.0	3.0	18.4	14.2	0.1	11.0	0.0	3.8	11.4	0.8	6.4
Maximum	79.0	96.0	44.8	88.5	0.7	27.0	5.0	28.1	39.6	12.8	21.1

ST: stroke time (months); BMI: body mass index (kg/m^2); TUGT: timed up and go test (time in s); GST: gait speed test in 10 m (m/s); FMS: Fugl-Meyer scale – lower limb section (0-28); MAS: Modified Ashworth Scale (0-5); ESp: extensors muscle strength paretic side (kgf); ESnp: extensors muscle strength non-paretic side (kgf); FSp: flexors muscle strength paretic side (kgf): FSnp: flexors muscle strength non-paretic side (kgf).

Table 4. Correlation analysis of the group with worst performance (GST < 0.80 m/s)

	Age	ST	BMI	TUGT	FMS	MAS	ESp	ESnp	FSp	FSnp
r	0.27	–0.26	–0.03	–0.87	0.69	–0.61	0.55	0.30	0.39	0.13
p	0.316	0.335	0.928	0.000	0.004	0.010	0.026	0.257	0.135	0.637

ST: stroke time (months); BMI: body mass index (kg/m^2); TUGT: timed up and go test (time in s); FMS: Fugl-Meyer scale – lower limb section (0-28); MAS: Modified Ashworth Scale (0-5); ESp: Extensors muscle strength paretic side (kgf); ESnp: Extensors muscle strength non-paretic side (kgf); FSp: Flexors muscle strength paretic side (kgf); FSnp: flexors muscle strength non-paretic side (kgf).

in a study by Sheffler et al.[29], where the influence of body mass on hemiparetic gait was evaluated. Although overweight may negatively affect post-stroke gait, the authors find no association between BMI and specific spatial-temporal parameters, including GS, cadence, double support time, or step length when measured over short distances.

Muscle strength and endurance seem to play a special role for good performance in this function, and this directly affects the functional capacity[6]. Although the paretic side is the most affected in relation to muscle strength, the non-paretic side may also show reduced strength. In individuals affected by stroke, the strength deficits range from 17% to 40% on the paretic side and from 5% to 40% on the non-paretic side. It is worth noting that this asymmetry of strength can also occur in healthy people, but in a smaller proportion (up to 10%)[27].

In a study conducted by Hyun et al.[30], the strength of the knee extensors and the dynamic balance was evaluated as predictors of walking in hemiparetic patients due to stroke in the acute phase. Fifty-three patients participated in the study, who were stratified in domestic ambulators (GST < 0.4 m/s) and community ambulators (GST > 0.4 m/s). The function of balance and functional mobility was evaluated using the Berg Balance Scale and the TUGT, respectively. The strength of the extensors and flexors knee was measured with an isokinetic dynamometer. The results found in the study indicate that the balance and strength of the knee extensors are the strongest predictors for the gait function of patients. However, the authors point out that the results may vary according to the severity of the gait. These findings corroborate those obtained in our study, where in the group with the best performance in GST (> 0.8 m/s), there was a strong and significant correlation ($r \geq 0.80$) of both muscle groups, flexors and extensors knee on the paretic side. Moreover, for the other group, with poorer performance in GST (< 0.8 m/s), the extensors knee strength also showed significant correlation.

Still regarding the evaluation of muscle strength, it is important to comment on the asymmetry found between the paretic and non-paretic sides. In the group with the

best performance in GST, there was less asymmetry, 26.7% in the extensors muscles knee and 34.2% lower in the flexors muscles side than in the non-paretic side. In the group with the worst performance in GST, this asymmetry is remarkable. An asymmetry of 45.9% was found in the extensors muscles and 58.1% in the flexors muscles in relation to the non-paretic side. In some cases, this asymmetry is even higher than that observed in the literature[27].

As for spasticity, as noted above, only the extensors muscles knee was evaluated by the MAS. This muscle usually presents an abnormal hyperactivity, which manifests, especially in the balance phase, during acceleration and intermediate balance of gait[31]. Spasticity is considered a common manifestation that results from abnormal neuroplasticity and intrinsic changes in the affected muscles[32]. Wissel et al.[33] pointed out that the presence of spasticity is associated with complaints of pain, greater impairment of muscle strength, and lower levels of functional independence. Our study corroborates these findings and indicates that this combination of higher degrees of spasticity with higher strength deficit is indicators of worse performance.

Another parameter that is strong and significantly related to the performance in GST is functional mobility, which in this study was evaluated by TUGT. Persson et al.[34] indicated that the TUGT is a sensitive test to detect changes in functional mobility in this special population, through time. This test is practical, fast, and low cost and has been widely used, especially in the elderly and hemiparetic patients evaluation. It allows estimating performance in several daily tasks such as getting up from a chair, walking, turning on one's own axis, and sitting down[35].

Conclusion

The study shows that there is a strong and significant relationship between GS and the degree of paresis, spasticity, and functional mobility.

The combination of an important motor deficit ex pressed by greater asymmetry of strength muscle between the paretic and non-paretic sides, and a greater degree of spasticity indicates worse gait performance.

We must improve evaluation of strength and tonus muscle to develop programs that emphasize increased strength and management of spasticity. A careful evaluation, followed by an adequate intervention, will certainly bring benefits to the locomotion these patients, and this is crucial to achieve this goal so desired by patients seeking a rehabilitation service.

These results should be viewed with caution, as the small number of patients evaluated is a limitation. New studies should be carried out with a larger number of participants, as well as the analysis of other variables not controlled here.

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Conflicts of interest

None to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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 have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Araújo JP, Darcis JV, Tomas AC, Mello WA. Mortality trend due to cerebrovascular accident in the city of Maringá, Paraná between the years of 2005 to 2015. Int J Cardiovasc Sci. 2018;31:56-62.
2. Flansbjer UB, Downham D, Lexell J. Knee muscle strength, gait performance, and perceived participation after stroke. Arch Phys Med Rehabil. 2006;87:974-80.
3. Lopes PG, Lopes JA, Brito CM, Alfieri FM, Rizzo Battistella L. Relationships of balance, gait performance, and functional outcome in chronic stroke patients: a comparison of left and right lesions. Biomed Res Int. 2015;2015:716042.
4. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". J Geriatr Phys Ther. 2009;32:46-9.
5. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci. 2013;68:39-46.
6. Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38:2096-100.
7. Thomas JR, Nelson JK, Silverman SJ. Métodos de Pesquisa em Atividade Física. 6th ed. Porto Alegre: Artmed; 2012.
8. Bertolucci PH, Brucki SM, Campacci SR, Juliano Y. O mini-exame do estado mental em uma população geral: impacto da escolaridade. Arq Neuropsiquiatr. 1994;52:1-7.
9. World Health Organization. WHO Steps Stroke Manual: the WHO Step Wise Approach to Stroke Surveillance. Geneva: World Health Organization; 2006.
10. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7:13-31.

11. Heidari M, Abootalebi C, Hosseini SA. Validity of modified ash worth scale as a measure of wrist spasticity in stroke patients. Iran Rehabil J. 2011;9:26-30.
12. Podsiadlo D, Richardson S. The timed "Up and Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39:142-8.
13. Soares AV, Matos FM, Laus LH, Suzuki S. Estudo comparativo sobre a propensão de quedas em idosos institucionalizados e não institucionalizados através do nível de mobilidade funcional. Fisioter Bras. 2003;4:12-6.
14. Hafsteinsdóttir TB, Rensink M, Schuurmans M. Clinimetric properties of the timed up and go test for patients with stroke: a systematic review. Top Stroke Rehabil. 2014;21:197-210.
15. Chen CL, Chang KJ, Wu PY, Chi CH, Chang ST, Cheng YY. Comparison of the effects between isokinetic and isotonic strength training in subacute stroke patients. J Stroke Cerebrovasc Dis. 2015;24:1317-23.
16. Huh JS, Lee YS, Kim CH, Min YS, Kang MG, Jung TD. Effects of balance control training on functional outcomes in subacute hemiparetic stroke patients. Ann Rehabil Med. 2015;39:995-1001.
17. Isho T, Usuda S. Association of trunk control with mobility performance and accelerometry-based gait characteristics in hemiparetic patients with subacute stroke. Gait Posture. 2016;44:89-93.
18. Faria CD, Teixeira-Salmela LF, Silva EB, Nadeau S. Expanded timed up and go test with subjects with stroke: reliability and comparisons with matched healthy controls. Arch Phys Med Rehabil. 2012;93:1034-8.
19. Piva SR, Fitzgerald GK, Irrgang JJ, Bouzubar F, Starz TW. Get up and go test in patients with knee osteoarthritis. Arch Phys Med Rehabil. 2004;85:284-9.
20. Martins JC, Aguiar LT, Lara EM, Moura JB, Souza LA, Teixeira-Salmela LF, et al. Assessment of the strength of the lower limb muscles in subjects with stroke with portable dynamometry: a literature review. Fisioter mov. 2016;29:193-208.
21. Souza LA, Martins JC, Teixeira-Salmela LF, Lara EM, Moura JB, Aguiar LT, et al. Validity and reliability of the modified sphygmomanometer test to assess strength of the lower limbs and trunk muscles after stroke. J Rehabil Med. 2014;46:620-8.
22. Cooper A, Alghamdi GA, Alghamdi MA, Altowaijri A, Richardson S. The relationship of lower limb muscle strength and knee joint hyperextension during the stance phase of gait in hemiparetic stroke patients. Physiother Res Int. 2012;17:150-6.
23. Akbari A, Karimi H. The effect of strengthening exercises on exaggerated muscle tonicity in chronic hemiparesis following stroke. J Med Sci. 2006;6:382-8.
24. Correa CS, da Silva BG, Alberton CL, Wilhelm EN, Moraes DA, Lima CS, et al. Análise da força isométrica máxima e do sinal de EMG em exercícios para os membros inferiores. Rev Bras Cineantropom Desempenho Hum. 2011;13:429-5.
25. Kiyama R, Fukudome K, Hiyoshi T, Umemoto A, Yoshimoto Y, Maeda T. The loss of dexterity in the bilateral lower extremities in patients with stroke. J Appl Biomech. 2011;27:122-9.
26. Iwabe C, Diz MA, Barudy DP. Análise cinemática da marcha em indivíduos com acidente vascular encefálico. Rev Neurociênc. 2008;16:292-6.
27. Signal NE. Strength training after stroke: rationale, evidence and potential implementation barriers for physiotherapists. N Z J Physiother. 2014;42:101-7.
28. Beavers KM, Beavers DP, Houston DK, Harris TB, Hue TF, Koster A, et al. Associations between body composition and gait-speed decline: results from the health, aging, and body composition study. Am J Clin Nutr. 2013;97:552-60.
29. Sheffler LR, Bailey SN, Gunzler D, Chae J. Effect of body mass index on hemiparetic gait. PM R. 2014;6:908-13.
30. Hyun CW, Han EY, Im SH, Choi JC, Kim BR, Yoon HM, et al. Hemiparetic knee extensor strength and balance function are predictors of ambulatory function in subacute stroke patients. Ann Rehabil Med. 2015;39:577-85.
31. Boudarham J, Roche N, Pradon D, Delouf E, Bensmail D, Zory R. Effects of quadriceps muscle fatigue on stiff-knee gait in patients with hemiparesis. PLoS One. 2014;9:e94138.
32. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. Front Hum Neurosci. 2015;9:192.
33. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. J Neurol. 2010;257:1067-72.
34. Persson CU, Danielsson A, Sunnerhagen KS, Grimby-Ekman A, Hansson PO. Timed up and go as a measure for longitudinal change in mobility after stroke - postural stroke study in gothenburg (POSTGOT). J Neuroeng Rehabil. 2014;11:83.
35. Soares AV, Marcelino E, Borges NG Jr., Domenech SC, Loch MS, Sagawa Y Jr. Relação entre dinapenia, sarcopenia e mobilidade funcional em idosos frágeis institucionalizados. Medicina (Ribeirão Preto). 2016;49:195-201.

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ORIGINAL ARTICLE

Prevalence of comorbidities in children with attention deficit/hyperactivity disorder: Measured and systematic review of care health studies

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Abstract

Background and objectives: *Children and adolescents with a diagnosis of attention deficit hyperactivity disorder demonstrate a developmental delay in emotional and social functions, sleep difficulties, enuresis, and/or paroxysms in electroencephalographic measurements.The purpose of the study is to know if there is an association between comorbidities and ADHD.The second objective was to compare the results with previous studies in different countries.* **Material and methods:** *Retrospective analysis of a clinical database (CDB) was conducted identifying 1049 Spanish children and adolescents diagnosed with ADHD according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) in the Department of Pediatrics of the Hospital Universitario Dr. Peset.* **Results:** *In the 297 CDB aged 6 - 16 years children included, the comorbidities were statistically significant.This medical conditions in Spanish children with ADHD coexist outside of Spain and are statistically significant in all aspects analyzed except in anxiety, Asperger's syndrome and enuresis.* **Conclusions:** *Our results support the association between comorbidities and ADHD. It is important for professionals to make sure that they identify different comorbidities during the diagnostic process as during the clinical follow-up.The article is recommended to teachers, therapists and health professionals, for adopting a proactive and intermodal team approach in the detection and treatment of comorbidities in children and youth.*

Key words: *Attention deficit hyperactivity disorder. Comorbidities. Detection. Diagnosis.*

Prevalencia de comorbilidades en niños con trastorno por déficit de atención/hiperactividad: revisión medida y sistemática de estudios de salud asistencial

Resumen

Antecedentes y objetivos: *Los niños y adolescentes con diagnóstico de Trastorno por Déficit de Atención/Hiperactividad (TDAH) presentan un retraso en el desarrollo de las funciones sociales y emocionales, dificultades para dormir, enuresis y/o paroxismos en las mediciones electroencefalográficas (EEG). El propósito del estudio es saber si existe una asociación entre las comorbilidades y el TDAH. El segundo objetivo fue comparar los resultados con estudios previos en diferentes*

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países. **Método:** *Se realizó un análisis retrospectivo de una base de datos de historias clínicas (CDB) que identificó a 1049 niños y adolescentes españoles diagnosticados con TDAH de acuerdo con el DSM-IV (Manual diagnóstico y estadístico de trastornos mentales) en el Departamento de Pediatría del Hospital Universitario Dr. Peset.* **Resultados:** *En las 297 CDB de niños con edades entre los 6 a 16 años, las comorbilidades fueron estadísticamente significativas. Estas condiciones médicas en niños españoles con TDAH coexisten fuera de España y han sido estadísticamente significativos en todos los aspectos analizados, excepto en ansiedad, síndrome de Asperger y enuresis.* **Conclusiones:** *Nuestros resultados apoyan la asociación entre comorbilidades y TDAH. Es importante que los profesionales se aseguren de identificar las diferentes comorbilidades durante el proceso de diagnóstico y durante el seguimiento clínico. El artículo se recomienda a maestros, terapeutas y profesionales de la salud para que adopten un enfoque de equipo proactivo e intermodal en la detección y tratamiento de comorbilidades en niños y jóvenes.*

Palabras clave: *Trastorno por déficit de atención/hiperactividad. TDAH. Comorbilidades. Detección. Diagnóstico.*

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder of childhood, and it is associated with social and academic difficulties and psychiatric comorbidities such as depression, anxiety, low self-esteem, and pervasive across settings can cause problems in the daily activities of a child as well as later in their adult life[1]. In addition, studies detected difficulties in behavioral regulation and emotional stability in children younger than 2 years of age who were later diagnosed diagnosis with ADHD[2]. ADHD during childhood is one of the most common causes of school failure and social problems. It is a disorder that can persist and manifest in adulthood in more than 60% of cases. Several studies have found that the quality of life in adolescents and in adults who were diagnosed with ADHD during their childhood is clearly related to the severity of comorbidities symptoms[3]. In studies with adults who have a residual form of this disorder, the research has found a higher frequency of behavioral abnormalities in labor activities and in family relationships, substance abuse, accidents, and crime[4]. Depression during childhood and adolescence also predicts negative outcomes in adulthood such as stressful life events, low social support, and low satisfaction with life[5]. Maternal depression and concurrent symptoms at 4-6 years of age predict which children with ADHD are at greatest risk for depression and/or suicidality as adolescents[6]. A diagnosis of both ADHD and depression is associated with the most significant deficiencies for either disorder than one alone. For example, young people with ADHD and depression have an increased risk of developing bipolar disorder and oppositional defiant disorder, and require much more intensive interventions compared to young people with ADHD but without depression[5]. Interventions for both diagnoses also report more psychosocial and family problems as well as higher levels of stress[7,8]. Despite the impact of ADHD and depressive symptoms in young people, few studies have examined the underlying mechanisms which contribute to the emergence of these symptoms[9]. One promising mechanism is emotion regulation (ER), as the deficit in the ability of ER has been associated with young children with ADHD and with depressive symptoms. This point is primarily relevant for young people with ADHD symptoms as it emphasizes the role of effort in control – the deliberate modulation of emotional states, emotional regulation, and subsequent behaviors, which involve the ability to focus deliberately, divert attention, hyperactivity, and inhibit or activate an appropriate behavior[10-12]. Several studies suggest that young people with ADHD demonstrate an inability to continue a task when frustrated or they have an inability to seek help from their parents. In extreme levels, when they are solving more limited problems, they focus more on negative aspects of a task compared to healthy controls. Young people with ADHD also have difficulties identifying and processing negative emotions and high-stress exposure between childhood and young adulthood is strongly intertwined with a persistent course of ADHD and with comorbid problems taking the form of severe and persistent emotion dysregulation (irritability, extreme reactivity, and frustration) or elevated and increasing irritability, anxiety, and depression[13,14]. Longitudinal research has shown that the ADHD diagnosis persists into adulthood, participants manifest higher levels of impulsive emotions (defined by symptoms such as low tolerance to frustration, impatience, and irritability) compared to those who do not have ADHD as an adult. This situation contributes to deficits in family, peer, financial, and labor relationships[15]. When comparing subtypes, children with inattentive ADHD have a higher rate in eating disorders, anxiety, and depression than in those with hyperactive and/or combined ADHD. In this both hyperactive and combined ADHD, children often have social problems, as they take things that do not belong to them,

do not wait their turn, and act without considering before the feelings of others. Children with ADHD inattentive type, rather, tend to be socially isolated, self-absorbed, and most likely have an introverted behavior[16] (Diamond, 2005). ADHD without hyperactivity and ADHD with hyperactivity are two different disorders with different cognitive and behavioral profiles, different patterns of comorbidities, different responses to medication, and different underlying neurobiology[16] characteristics that become chronic and progressively worse (i.e., findings support the diagnosis of ADHD in younger children by demonstrating that the symptoms and associated impairment are likely to persist well into elementary school)[17]. It is unclear whether the features of anxiety and ADHD are possible to identify very early of age; for example, in one child, his emotional deregulation at 18 months of age was associated with symptoms of anxiety and ADHD at 3 years of age. The study could not confirm if the emotional deregulation at 18 months predicts the cooccurrence of anxiety and ADHD symptoms. This implies that the identification risk at 18 months is a clinical challenge. By identifying early, there is a risk of over-identification and treatment of preschool children who are not going to develop ADHD or anxiety in their immediate future[18]. However, longitudinal studies in school-age children found continuity of symptoms for anxiety and ADHD[19,20]. In children with ADHD with an anxiety disorder have more than 50% of them also oppositional defiant disorder or conduct disorder[21].

The relationship between ADHD and sleep disorders is unclear. According to a categorical approach, specific sleep disorders are a common comorbidity in children with ADHD. Those with ADHD more often display hypopnea and/or apnea, movements in peripheral limbs during sleep, insomnia, and narcolepsy which could result in significant functional impairments that affect mood, attention, behavior, and ultimately school/work performance and quality of life[22]. Polysomnography shows an increased latency in sleep onset of families ADHD children report less maintenance and duration of sleep, resistance by the child at bedtime, difficulties in sleep onset, difficult in nocturnal breathing, enuresis, nocturnal awakenings, and difficulty in waking up in the morning and daytime sleepiness[23]. In another multicenter cross-sectional study in 12 Spanish hospitals, neurologists reported that sleep disorder affects less than a quarter of patients (24.5%) and up to 23% stated that the prevalence was < 10%, while between 58% and 92% of parents of patients attending consultations in pediatric neurology report that their children have some aspect disturbed in the sleep. Although most neurologists appreciate the importance of diagnosis and treatment of sleep disorders in children with neurological disorders, it is often underestimated and therefore essential to include in ADHD evaluations as proper and early treatment would improve symptoms and the quality of life in patients and families[24].

Moreover, many children with ADHD develop epilepsy. In one study of 23 patients with epilepsy, 19 of them had ADHD symptoms preceding the onset of seizures[25]. An epidemiological study showed that the risk of epilepsy is 2.5 times higher in children who have already developed symptoms of ADHD[26]. With regard to abnormal electroencephalographic (EEG) recordings outside epilepsy, a recent study found abnormal EEG readings in 19 of 50 children diagnosed with ADHD. The most abnormal results were in focal and generalized paroxysms of sharp waves in phase opposition and slow waves. The most frequent location of EEG abnormalities was in the temporal lobe (45%), although there were focal paroxysms in other lobes; 28% in the right temporal region, 17% in the left temporal region, and 22% in the left frontal lobe, followed by 11% in the left parietal region[27].

In children's ADHD diagnosis, enuresis is a relatively new clinical aspect and is part of our ongoing effort to better understand comorbidities. Children with ADHD are more likely than their peers without ADHD to develop enuresis with a similar trend for encopresis and comorbid enuresis implying an immaturity in the developing nervous system of children who have this combination of problems[28]. Children with primary nocturnal enuresis (PNE) show a significant reduction in activity in the left posterior cerebellum compared to controls without PNE[29]. Similarly, functional magnetic resonance imaging (fMRI) demonstrated low activation in the right prefrontal cortex and increased activity in the left hemisphere during inhibition of motor response compared to controls without PNA, indicating abnormal network brain areas during response inhibition in children with PNE[30].

Therefore, this study aims to characterize the diagnostic complexity of children and adolescents who receive a diagnosis of ADHD. These findings could be helpful to develop guidelines that reflect the needs of children with ADHD. We treat a review of the comorbidities in itself complex in the diagnosis of ADHD.

Methods

Participants

Retrospective analysis of a clinical database (CDB) was conducted identifying 1049 Spanish children and

Table 1. Total excluded and included

226 participants born since 1990 and 1998
379 participants without an interdisciplinary diagnosis
14 participants had ADS
47 participants had a neurological disease diagnosed as epilepsy, brain traumatic
9 participants had a genetic syndrome diagnosed as deletions
26 participants coming from national or international adoptions or born in Spain of foreign parents
39 participants had not neurophysiological studies (EEG, qEEG, and ERPs)
12 participants without approach less medical data
Total included
297 participants met the clinical criteria

ADS: autism spectrum disorder; EEG: electroencephalographic; qEEG: quantitative EEG; ERPs: event-related potentials.

adolescents diagnosed with ADHD according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) in the Department of Pediatrics of the Hospital Universitario Dr. Peset. The comorbidities were diagnosed in the corresponding medical service (Pediatrics, Mental Health, Neurology). Personal and clinical data of patients were reviewed to determine those who met the clinical criteria previously established and described below. After eliminating patients who did not meet for the above, 297 CDB aged 6-16 years of children (79 females and 218 males; mean age, 09.10 years) diagnosed with ADHD were used for this study.

Inclusion criteria

- Patients diagnosed with ADHD born in Spain from January 1999 to December 2009.
- Patients diagnosed with ADHD with intelligence quotient (IQ) of 80 or higher with Spanish parents.
- Patients diagnosed with ADHD who attended medical appointments.

Exclusion criteria

- Patients diagnosed with ADHD born and raised from January 1999 to December 2009 in Spain with IQ below 80.
- Patients aged in or outside the range 6-15 years and 11 months adopted or born and raised in Spain of foreign parents
- Patients diagnosed with ADHD who not attended medical appointments.
- Patients diagnosed with ADHD who later acquired brain injury, surgery, and/or neurological diseases such as traumatic brain injury, epilepsy, and/or Gilles de la Tourette Syndrome (Table 1).

In the following table are described by the participants:

Medical data related to the child were recorded in a confidential database for exclusive use of the project. Data about diagnosis, treatments, personal circumstances, and about clinical evolution were collected according to the law 15/99 on protection of personal data.

Statistical analysis

First, descriptive statistics as comorbidity prevalence of the different pathologies studies and their confidence interval 95% were calculated. The relationships between the categorical variables the prevalence of ADHD child's comorbidity with the ADHD child's without comorbidity were analyzed using the Chi-square test ($p < 0.05$) by each comorbidity studied. Finally, a comparison of each comorbidity prevalence identify was also compared through the review of outside studies from other countries; it was analyzed using the Chi-square test ($p < 0.05$). Statistical analyses were conducted using IBM SPSS Statistics 25.

Results

Many children diagnosed with ADHD have comorbidities. In Spain, children and adolescents diagnosed with ADHD, the current study found that all potential comorbid conditions were statistically significant in the aspects analyzed ($p \leq 0.001$) (Table 2). When examining outside studies, results on the presence or absence of conditions that coexist in children diagnosed with ADHD outside of Spain are statistically significant in all aspects analyzed ($p \leq 0.001$), except in anxiety, and in Asperger's disease[31] and in female and male Enuresis[32] (Table 2a).

Discussion

In this study in ADHD, 25% of patients showed social problems, 28% depression and/or anxiety, and 19% had difficulties in the maintenance of nighttime sleep. The results were associated with those obtained by Hoza[12], Mellon[28], and Sheerman[32] in United States of America, by Chou in China[33], by Fonseca in Brazil[34],

Table 2. Prevalence of comorbidities in children with attention deficit hyperactivity disorder for the sample (n = 297)

Variable	Frequency (n)	Prevalence (%)	Prevalence (95% CI)	Chi-square test (p)
Peer/dyadic relationship difficulties	74	25.00	20.18-30.31	≤ 0.001
Depression/anxiety	83	28.00	23.62-34.18	≤ 0.001
Anxiety	41	14.00	10.48-18.74	
Sleep disorders	56	18.90	15.87-25.31	≤ 0.001
Insomnia for lack of limits on family	7	2.35	1.25-5.44	≤ 0.001
Nocturnal enuresis	15	5.10	2.95-8.36	≤ 0.001
Snorer	3	1.01	0.26-3.17	≤ 0.001
Nighttime awakenings	11	3.70	1.95-6.71	≤ 0.001
Delay sleep onset syndrome	3	1.01	0.26-3.17	≤ 0.001
Restless leg syndrome	3	1.01	0.26-3.17	≤ 0.001
Bruxism	3	1.01	0.26-3.17	≤ 0.001
Catathrenia (night whimper)	4	1.70	0.43-3.64	≤ 0.001
Night terrors	2	0.70	0.11-2.67	≤ 0.001
Somniloquy	5	1.70	0.62-4.10	≤ 0.001
Epilepsy (EEG)	72	24.35	19.69-29.79	≤ 0.001
Primary nocturnal enuresis	10	3.37	1.72-6.29	
Female	2	0.67	0.11-2.67	
Male	8	2.70	1.25-5.44	0.055

ANOVA test: $p < 0.01$. RF: relative frequency; %: proportion; 95% CI: Confidence Interval 95%; p: Fisher values; EEG: encephalogram.

Table 2a. Comorbidities in children with attention deficit hyperactivity disorder according to previous studies

Variable	Frequency (n)	Prevalence (%)	Prevalence (95% CI)	Chi-square test (p)	Previous studies
Peer/dyadic relationship difficulties	92	56.00	47.83-63.41	≤ 0.001	Hoza, 2005
Depression	10	6.70	3.59-12.82	0.029	Bauermeister, 2007
Depression	68	21.30	17.03-23.30	0.020	Silva, 2015
Anxiety	34	23.77	17.23-31.75	0.012	Bauermeister, 2007
Anxiety	169	52.60	47.34-58.54	≤ 0.001	Silva, 2015
Anxiety	12	11.90	6.55-20.20	0.665	Ogrim, 2012
Asperger syndrome (symptoms)	5	4.95	1.83-11.71	0.148	Ogrim, 2012
Sleep disorders	45	31.46	24.10-39.84	0.003	Bauermeister, 2007
Epilepsy 6-18 years old (EEG)	2843	15.63	15.10-16.17	≤ 0.001	Chou, 2013
Epilepsy 8-11 years old (EEG)	3	10.00	2.61-27.67	0.095	Fonseca, 2008
Primary nocturnal enuresis	100	9.00	7.25-10.63	0.044	Shreeram, 2009
Female	32	2.51	1.95-4.00	0.198	
Male	68	6.21	4.70-7.56	0.216	
Primary nocturnal enuresis	35	12.10	6.99-13.45	≤ 0.001	Mellon, 2013
Primary nocturnal enuresis	165	17.60	15.02-19.94	0.010	Joinson, 2007

ANOVA test: $p < 0.01$ (11, 20, 8, 33, 34, 28, 35); $p \leq 0.05$ (31, 32). RF: relative frequency; %: proportion; 95% CI: Confidence Interval 95%; p: Fisher values; EEG: electroencepham.

by Joinson in United Kingdom[35], by Silva in Australia[9], and by Bauermeister in Puerto Rico[20].

Children with ADHD often have conflicts with adults and peers, and suffer from unpopularity, rejection by peers, and a lack of friendships, in part as a consequence of their ADHD symptoms. In summary, social relations are also one of the biggest problems in children with ADHD. Parents, teachers, and their own colleagues systematically report that those with ADHD can be aggressive, intrusive, disruptive, manipulative, and less able to communicate and socialize effectively[11,13,36]. Some studies reported little difference and related problems between genders[20].

Parents with ADHD children compared with normative data reported more problems in terms of emotional-behavioral role function, behavior, mental health, and self-esteem. Children with multiple comorbidity disorders have poorer psychosocial health-related quality of life across a range of domains compared with children with none and one comorbid disorder[4]. In addition, compared to children who have no comorbidities, psychosocial health-related quality of life was significantly lower in children with comorbid oppositional defiant disorder or conduct disorder, but not in children with a comorbid learning disorder[4]. In summary, social relations are one of the biggest problems in children with ADHD.

Sleep disorders may also induce symptoms of ADHD and are believed to be the result of excessive daytime sleepiness. However, it may be difficult for the clinical professional to recognize differences between the comorbidity from one sleep disorder to similar symptoms in ADHD[37,38]. We found abnormal results in 24.35% of patients; therefore, the EEG is a valid study in the valuation process for test underlying or comorbid epilepsy in children with ADHD. Epilepsy and ADHD can affect social, educational, and emotional life. The association between ADHD and epilepsy is of great interest in many studies published recently because children with epilepsy have a significant risk in presenting ADHD, and often display deficits in the performance of working memory[26,33,39]. Studies have detected significant similarities between epilepsy and ADHD in males (citation). ADHD with or without epilepsy may share a common abnormal and underlying neurobiological cause[40].

In our study, the PNE in children with ADHD was in 5.05%, we consider the increase of psychological problems reported by parents of children with enuresis compared to those children without enuresis, and the possible pathogenic etiological between ADHD and incontinence according to neurophysiological and neuroimaging results[30]. However, enuresis is difficult to treat and show lower compliance. Given results in the treatment in incontinence are appreciated in the relevant clinical data regarding ADHD and enuresis, this appears to be a main comorbid condition that should be evaluated and specifically address in ADHD children[40].

Conclusions

The current study carried out a broad and comprehensive characterization of comorbidities in children and adolescents with ADHD in an effort to promote appropriate clinical decision making and reduced confusion. Detection and resolution of depressive symptoms, anxious symptoms, and/or difficulties in sleep in those diagnosed with ADHD may reduce emotional risk and morning fatigue. It is very important to detect these symptoms to decrease social and cognitive consequences. Finally, using EEG in this population provides greater assessment and diagnosis of complex developmental disorders such as ADHD.

Study limitations

First, we recruited data about ADHD comorbidities from different medical specialties departments at the hospital. Our findings should be interpreted in light of limitations. Accordingly, we were unable to stratify symptoms according to high- and low-comorbidity. Second, we were not able to test whether comorbidities are unique to children with ADHD or are also observed in other disorders such as depression and learning delay. Future studies are needed about the relationship between comorbidities and ADHD.

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Conflicts of interest

The authors declare that they have 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 no patient data appear in this article.

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

References

1. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. Arch Dis Child. 2005;90 Suppl 1:i2-7.
2. Magallón S, Crespo-Eguílaz N, Ecay M, Poch-Olivé ML, Narbona J. Estilo comportamental al inicio del segundo año de vida: estudio retrospectivo en escolares afectados de trastorno por déficit de atención e hiperactividad. An Pediatr. 2009;70:562-9.
3. Klassen AF, Miller A, Fine S. Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. Pediatrics. 2004;114:e541-7.
4. McGough JJ, Smalley SL, McCracken JT, Yang M, Del'Homme M, Lynn DE, et al. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. Am J Psychiatry. 2005; 162:1621-7.
5. Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCREARY M, et al. New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. J Am Acad Child Adolesc Psychiatry. 2008;47:426-34.
6. Chronis-Tuscano A, Molina BS, Pelham WE, Applegate B, Dahlke A, Overmyer M, et al. Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2010;67:1044-51.
7. Bussing R, Mason DM, Bell L, Porter P, Garvan C. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. J Am Acad Child Adolesc Psychiatry. 2010;49:595-605.
8. Silva D, Houghton S, Hagemann E, Bower C. Comorbidities of attention deficit hyperactivity disorder: pregnancy risk factors and parent mental health. Community Ment Health J. 2015;51:738-45.
9. Martel MM, Nigg JT. Child ADHD and personality/temperament traits of reactive an effortful control resiliency and emotionality. J Child Psychol Psychiatry. 2009;46:1437-44.
10. Seymour KE, Chronis-Tuscano A, Iwamoto DK, Kurdziel G, Macpherson L. Emotion regulation mediates the association between ADHD and depressive symptoms in a community sample of youth. J Abnorm Child Psychol. 2014;42:611-21.
11. Landis TD, Garcia AM, Hart KC, Graziano PA. Differentiating symptoms of ADHD in preschoolers: the role of emotion regulation and executive function. J Atten Disord. 2020;Jan 6:1087054719896858.
12. Hoza B, Mrug S, Gerdes AC, Hinshaw SP, Bukowski WM, Gold JA, et al. What aspects of peer relationships are impaired in children with attention-deficit/hyperactivity disorder? J Consult Clin Psychol. 2005;73:411-23.
13. Hartman CA, Rommelse N, van der Klugt CL, Wanders RB, Timmerman ME. Stress exposure and the course of ADHD from childhood to young adulthood: comorbid severe emotion dysregulation or mood and anxiety problems. J Clin Med. 2019;8:E1824.
14. Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. J Am Acad Child Adolesc Psychiatry. 2010;49:503-13.
15. Diamond A. Attention-deficit disorder (attention-deficit/hyperactivity disorder without hyperactivity): a neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). Dev Psychopathol. 2005;17:807-25.
16. Lahey BB, Pelham WE, Loney J, Kipp H, Ehrhardt A, Lee SS, et al. Three-year predictive validity of DSM-IV attention deficit hyperactivity disorder in children diagnosed at 4-6 years of age. Am J Psychiatry. 2004;161:2014-20.
17. Overgaard KR, Aase H, Torgersen S, Reichborn-Kjennerud T, Oerbeck B, Myhre A, et al. Continuity in features of anxiety and attention deficit/hyperactivity disorder in young preschool children. Eur Child Adolesc Psychiatry. 2014;23:743-52.
18. Larsson H, Dilshad R, Lichtenstein P, Barker ED. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. J Child Psychol Psychiatry. 2011;52:954-63.
19. Bauermeister JJ, Bird HR, Shrout PE, Chavez L, Ramírez R, Canino G. Short-term persistence of DSM-IV ADHD diagnoses: influence of context, age, and gender. J Am Acad Child Adolesc Psychiatry. 2011;50:554-62.
20. Shea CK, Lee MM, Lai KY, Luk ES, Leung PW. Prevalence of anxiety disorders in Hong Kong Chinese children with ADHD. J Atten Disord. 2018;22:403-13.
21. Wajszilber D, Santiseban JA, Gruber R. Sleep disorders in patients with ADHD: impact and management challenges. Nat Sci Sleep. 2018;10:453-80.
22. Vila MT, Torres AM, Soto BB, Gomar MR, Langa MJ, Sierra AI. Relación entre el trastorno por déficit de atención e hiperactividad y los trastornos del sueño. Resultados de un estudio epidemiológico en la población escolar de la ciudad de Gandía. An Pediatr. 2008;69:251-7.
23. Pérez-Villena A, Soto-Insuga V, Castaño-De la Mota C, Martín-Del Valle F, Pons-Rodríguez M, Lozada-Del Pozo M. Importancia de los problemas de sueño en los niños con cefalea y otros trastornos del neurodesarrollo en las consultas de neuropediatría. Rev Neurol. 2016;62:61-7.
24. Hermann B, Jones J, Dabbs K, Allen CA, Sheth R, Fine J, et al. The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. Brain. 2007;130:3135-48.
25. Sand T, Breivik N, Herigstad A. Assessment of ADHD with EEG. Tidsskr Nor Laegeforen. 2013;133:312-6.
26. Cornelio-Nieto JO, Borbolla-Sala ME, Gallegos-Dimas A. Alteraciones electroencefalográficas en niños con trastorno por déficit de atención/hiperactividad. Rev Neuro. 2011;52 Suppl 1:S97-101.
27. Mellon MW, Natchev BE, Katusic SK, Colligan RC, Weaver AL, Voigt RG, et al. Incidence of enuresis and encopresis among children with attention-deficit/hyperactivity disorder in a population-based birth cohort. Acad Pediatr. 2013;13:322-7.
28. Yu B, Guo Q, Fan G, Ma H, Wang L, Liu N. Evaluation of working memory impairment in children with primary nocturnal enuresis: evidence from event-related functional magnetic resonance imaging. J Paediatr Child Health. 2011;47:429-35.
29. Lei D, Ma J, Du X, Shen G, Tian M, Li G. Altered brain activation during response inhibition in children with primary nocturnal enuresis: an fMRI study. Hum Brain Mapp. 2012;33:2913-9.
30. Ogrim G, Kropotov J, Hestad K. The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates. Psychiatry Res. 2012;198:482-8.
31. Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: results from a nationally representative study. J Am Acad Child Adolesc Psychiatry. 2009;48:35-41.
32. Chou IC, Chang YT, Chin ZN, Muo CH, Sung FC, Kuo HT, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. PLoS One. 2013;8:e57926.
33. Fonseca LC, Tedrus GM, Moraes Cd, Vicente Machado Ad, Almeida MP, Oliveira DO. Epileptiform abnormalities and quantitative EEG in children with attention-deficit/hyperactivity disorder. Arq Neuropsiquiatr. 2008;66:462-7.
34. Joinson C, Heron J, Butler R, Von Gontard A, Butler U, Emond A, et al. A United Kingdom population-based study of intellectual capacities in children with and without soiling, daytime wetting, and bed-wetting. Pediatrics. 2007;120:e308-16.
35. Mikami AY, Normand S. The importance of social contextual factors in peer relationships in children with ADHD. Curr Dev Disord Rep. 2015;2:30-7.
36. Walcott CM, Landau S. The relation between disinhibition and emotion regulation in boys with attention deficit hyperactivity disorder. J Clin Child Adolesc Psychol. 2004;33:772-82.
37. Bioulac S, Micoulaud-Franchi JA, Philip P. Excessive daytime sleepiness in patients with ADHD-diagnostic and management strategies. Curr Psychiatry Rep. 2015;17:608.
38. Hvolby A. Associations of sleep disturbance with ADHD: implications for treatment. Atten Defic Hyperact Disord. 2015;7:1-8.
39. Bechtel N, Kobel M, Penner IK, Specht K, Klarhöfer M, Scheffler K, et al. Attention-deficit/hyperactivity disorder in childhood epilepsy: a neuropsychological and functional imaging study. Epilepsia. 2012;53:325-33.
40. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. Eur Child Adolesc Psychiatry. 2015;24:127-40.

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REVIEW ARTICLE

Neurological manifestations associated with SARS-CoV-2 – A review

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Abstract

A new virus belonging to the Coronavirus (COV) family burst into the Wuhan region of China causing severe acute respiratory syndrome of high lethality. COV not only is pathogenic that mainly affects the human respiratory system but also has neuroinvasive capabilities. The transmission mechanism is person-to-person; also air propagation and other mechanisms have been described. The main entrance mechanism is through the binding of the virus' S protein with angiotensin-converting enzyme receptors, these are present in multiple systems including the nervous system. The spread of SARS-CoV-2 in systemic circulation or through the cribriform plaque of the ethmoid bone during an early or later phase of infection can lead to brain involvement. Multiple cases with general neurological manifestations have been reported worldwide, such as headache and confusion, but also more specific cases of cerebrovascular disease, encephalitis, and anosmia, among others described in this review. Specialists are encouraged, within patients with neurological manifestations, to investigate epidemiological links to establish the relationship between a neurological manifestation probably secondary to COVID-19. Diagnostic tests in patients with such manifestations are recommended to establish an association. It is recommended to conduct studies oriented to the different neurological manifestations, and also to clinicians to stay alert with them to improve both the evolution and the prognosis of the patient.

Key words: *Neurotropism. COVID-19. SARS-CoV-2. Manifestations. Central nervous system.*

Manifestaciones neurologicas asociadas a SARS-CoV-2: una revisión bibliografica

Resumen

Un nuevo virus perteneciente a la familia de los coronavirus irrumpió como agente patógeno en la región de Wuhan, China provocando un síndrome respiratorio agudo severo de alta letalidad. El coronavirus es patógeno que principalmente afecta al sistema respiratorio humano, pero también tiene capacidades neuroinvasivas. El mecanismo de transmisión es de persona a persona, también la propagación aérea y otros mecanismos se han descrito. El principal mecanismo de entrada es a través de la unión de la proteína S del virus con los receptores de enzima convertidora de angiotensina, estos presentes en múltiples sistemas incluyendo el sistema nervioso. La diseminación de SARS-CoV-2 en la circulación sistémica o a través de la placa cribiforme del hueso etmoides durante una fase temprana o posterior de la infección puede conducir a la afectación cerebral. Múltiples casos con manifestaciones neurológicas generales han sido reportados a nivel mundial, como ser cefalea y confusión, pero también casos más específicos de enfermedad cerebrovascular, encefalitis, anosmia entre otros

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que son descritos en esta revisión. Se recomienda a los especialistas que, en aquellos pacientes con manifestaciones neurológicas, que se investigue acerca de nexos epidemiológicos, para así establecer el vínculo entre una manifestación neurológica probablemente secundaria a COVID-19. Se recomienda realizar las pruebas de diagnóstico, en pacientes con dichas manifestaciones, para establecer una asociación. Se recomienda realizar estudios orientados a las diferentes manifestaciones neurológicas, y también a los clínicos a mantenerse alerta con las mismas para mejorar tanto la evolución como el pronóstico del paciente.

Palabras clave: *Neurotropismo. COVID-19. SARS-CoV-2. Manifestaciones. SNC.*

Introduction

In December 2019, a new virus belonging to the Coronavirus (CoV) family broke in as a pathogen in China's Wuhan region causing high-lethal severe acute respiratory syndrome (SARS). The World Health Organization (WHO) gave it the name SARS-CoV-2 given its similarity virologically and also in its clinical expression with SARS-CoV (229E [HCoV-229E]), responsible for a syndrome of similar characteristics also originating in animal markets in China in 2003[1]. As of 24 February 2020, more than 80,000 confirmed cases have been reported, including more than 2700 deaths worldwide, affecting at least 37 countries. The WHO declared it a global health emergency by the end of January 2020[2].

CoVs are members of the family Coronaviridae, wrapped viruses that possess extraordinarily large single-chain RNA genomes ranging from 26 to 32 kb in length[3]. An unknown that continues to be investigated is the recognition of the zoonotic origin of said virus, but due to its close similarity to bat CoVs, it is likely that these are the primary reservoir of the virus, since with the reappearance of this new class of CoV various studies was performed and SARS-CoV-2 was found to be 96% identical at the genome level to a bat CoV; the same study revealed that the virus belongs to the SARS-CoV species. This is how SARS-CoV is speculated to have been transmitted to humans from exotic animals in markets in the outbreak 18 years ago, while Middle East respiratory syndrome coronavirus (MERS-CoV) was transmitted from camels to humans[4].

Transmission from one person to another has been demonstrated, and the transmission mechanism is known to be by respiratory drops generated during coughs and sneezes by symptomatic patients, but may also occur by asymptomatic individuals and before symptoms onset[5]. Anderson et al. suggest transmission through aerosols predominantly < 1 μm, produced when speaking or with normal breathing by asymptomatic patients. It also suggests that aerosols may be a long-distance transmission vehicle due to suspension of aerosols in the air for several hours. All of the above related to survival time and distances, virus concentrations, effects of temperature and humidity, and the implications of aerosol size and viral load in contact with the respiratory tract[6]. Chan et al. report findings that suggest the transmission of person to person and that intercity spread of SARS-CoV-2 by air is possible[7].

In a cohort study conducted by Li et al.[8], SARS-CoV-2 has been reported in semen of the 38 patients undergoing the study[8]. Fecal-oral transmission has also been suggested and a vertical transmission mechanism has recently been proposed[9].

SARS-CoV-2 uses the angiotensin-converting enzyme (ACE2) as its main receptor, which is widely expressed in vascular endothelium, respiratory epithelium, alveolar monocytes, macrophages, and neurons (Fig. 1). Later in the course of the disease, COVID-19 resembles SARS in terms of viral replication in the lower respiratory tract, and generates secondary viremia, followed by an extensive attack on target organs expressing ECA2, such as the heart, kidney, gastrointestinal tract, and vast distal vasculature[10].

The clinical characteristics of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multiorgan dysfunction[11]. Symptoms that have been reported in particular are fever, dry cough, dyspnea, myalgia and fatigue, less frequent confusion, headache, pharyngeal pain, rhinorrhea, abdominal pain, diarrhea, nausea, and vomiting[9].

CoV is one of the main viruses that mainly affects the human respiratory system, but it also has neuroinvasive capabilities and can spread from the respiratory tract to the central nervous system (CNS)[12].

In January 2020, Chen et al. published a retrospective analysis based on 99 patients diagnosed with SARS-CoV-2 pneumonia at a hospital in Wuhan, China. Neurological symptoms presented were confusion (9%) and headache (8%)[13]. In addition, different studies have been reported that assert neurological manifestations secondary to SARS-CoV-2, so attention should be paid

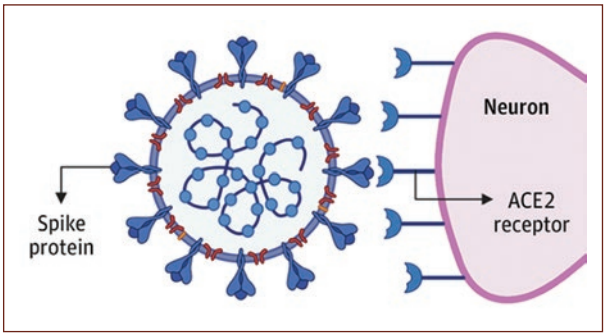

Figure 1. Angiotensin-converting enzyme (ACE)-2 receptors at a medullary junction to the SPIKE protein in severe acute respiratory syndrome coronavirus 2. Emerging data suggest that ACE 2 receptors are expressed in multiple regions of the human brain, including the motor cortex, posterior cingulate cortex, ventricles, Nigri substance, olfactory bulb, medium temporal turn, ventrolateral marrow, solitary tract nucleus, and vagus dorsal motor nucleus (*taken from Zubair et al.*[28]).

to these manifestations because they may affect the prognosis and evolution of the patient.

Neurotropism's background

It is currently known that CoVs are not always limited to the respiratory tract and that they can also invade CNS by inducing neurological diseases. This neuroinvasive capacity of CoVs has been documented almost for all COVs, including SARS-CoV, MERS-CoV, HCoV-229E, HCoV-OC43, mouse hepatitis virus, and porcine hemagglutinating encephalomyelitis[14].

The SARS pandemic that occurred in 2002 detected sequences of the virus genome in the brain of all SARS deceased autopsies with light microscopy, electron microscopy, and real-time reverse transcription-polymerase chain reaction (rRT-PCR). The signals were limited to the cytoplasm of numerous neurons in the hypothalamus and cortex[15]. The edema and scattered red degeneration of neurons were present in the brains of six of the eight confirmed cases of SARS. Viral SARS sequences and pathological changes were not present in the brain of unconfirmed cases or control cases[15]. Likewise, patients with acute SARS-CoV disease have also demonstrated the presence of the virus in cerebrospinal fluid[16].

Overall, neuroinvasive ability has been shown to be a common feature of COVs. Considering the high similarity between SARS-CoV and SARS-CoV-2, SARS-CoV-2 is also likely to have similar potential[14].

The spread of SARS-CoV-2 in systemic circulation or through the cribriform plaque of the ethmoid bone during an early or later stage of infection can lead to brain involvement as has been reported in the past for SARS-CoV[16]. The latter can be supported by the fact that in the study of Mao et al., some patients had hyposmia[17].

The presence of the COVID-19 virus in the general circulation allows it to, understandably, move to brain circulation where the slow flow of blood within microcirculation could be one of the factors that can facilitate the interaction of the spike protein (protein S) of the SARS-CoV-2 virus with ACE-2 receptors[16]. These receptors are known to be expressed in the lungs, heart, kidneys, intestines, brain, and testicles by converting these different organs into possible SARS-CoV-2 targets[16].

CNS manifestations

Inespecific manifestations

SARS-CoV-2 has been shown to exhibit non-specific neurological manifestations, which are well unknown whether they can be caused directly or indirectly by the virus. In a study by Mao et al., 214 patients, 88 (41.1%) and 126 (58.9%) they were not serious. Of these, 78 (36.4%) neurological manifestations involve CNS, peripheral nervous system, and skeletal muscles. Severe patients were more likely to develop neurological symptoms, especially acute cerebrovascular disease, altered consciousness, and muscle injuries[17,18]. It should be emphasized that headache is the most common neurological symptom in Wuhan, China according to study conducted by Guan et al.[19].

Furthermore, in a study conducted in two different intensive care unit (ICU) in France, 58 patients reported neurological findings; agitation was present in 40 patients (69%). A total of 26 out of 40 patients were observed to have confusion under the ICU Confusion Assessment Method. Diffuse signs of the corticoespinal tract such as muscle stretching hyperreflexia, aquileo clonus, and bilateral Babinski sign were present in 39 patients (67%). Of the patients who had been discharged, 15 out of 45 (33%) had a dysexecutive syndrome that consisted of inattention, disorientation, or poorly organized movements in response to the command[20].

These neurological manifestations have also been reported in Latin America. In Chile, a study was conducted with 922 positive cases (Table 1), of which 597 (64.8%) headache as a cardinal symptom, while only

Table 1. Main clinical findings in the first 922 cases of COVID 19 in Chile

Síntomas	n	%
Headache	597	64.8
Dyspnea	498	54.0
Cough	452	49.0
Thoracic pain	407	44.1
Fever	78	8.5
Abdominal pain	41	4.4
Myalgias	32	3.5

Adapted from Rodriguez-Morales et al., 2020[21].

8.5% and 49.0% had fever and cough, respectively, among other symptoms. The presence of headache in most of these patients may suggest the potential neurotropism and neurovirulence of SARS-CoV-2 as seen in other naturally neurotropic human CoVs such as SARS-CoV and HCoV-OC43 and –229E[21].

Several observational studies have looked at symptoms of the disease, but few have addressed neurological symptoms that go beyond headache and confusion[22].

Meningitis and encephalitis

The first case of aseptic encephalitis was reported in a 24-year-old patient, brought to the emergency by an ambulance due to a seizure accompanied by unconsciousness, presenting multiple generalized tonic-clonic epileptic seizures, and obvious neck stiffness. It was taken both nasopharyngeal and cerebral spinal fluid (CSF) samples and was diagnosed using RT-PCR technique by finding SARS-CoV-2 RNA in cerebrospinal fluid[23].

Interestingly, imaging findings were also found in this patient, reporting a brain magnetic resonance imaging (MRI) with hyperintensity along the wall of the right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus, suggesting the possibility of SARS-CoV-2 meningitis[23].

In the current pandemic, Xiang et al.'s team, the Beijing Ditan Hospital confirmed the presence of SARS-CoV-2 virus in cerebrospinal fluid in patients positive for COVID-19. The finding was made using genomic sequencing techniques, as well as clinically confirming viral encephalitis in patients. This provides a solid foundation for considering CoVs as causing encephalitis[18].

Positive COVID-19 patients have been reported, which usually present a clinical picture of meningitis/encephalitis, but with CSF RT-PCR tests for SARS-CoV-2 negative. Some authors argue that this happens because of the low inoculum that can occur in the CSF.

This is the case of a 64-year-old patient, who at the neurological examination indicated that the patient was impaired in mental state, with an alternating consciousness between lethargy and irritability. Both lower limbs showed positive ankle clonus, which was more pronounced in the left limb. The lower left limb was positive for Babinski's sign and Chaddock's sign; the lower right limb was suspected positive for Chaddock's sign. He also showed meningeous signs[24].

There is also a positive patient for COVID-19 who has impaired consciousness accompanied by marked meningeous signs and Babinski's sign. After a thorough neurological evaluation by experts, the diagnosis of SARS-associated encephalitis CoV-2 was established, even though the CSF sample test tested negative for SARS-CoV-2[25].

Encephalopathy

Encephalopathy is a transient brain dysfunction syndrome that manifests as an acute or subacute affectation of the level of consciousness. COVID-19-associated encephalopathy may be due to toxic and metabolic causes, and the effect of hypoxia or drugs. Another associated indirect mechanism is the presence of subclinical crises[26]. Encephalopathy is a demonstration of how CNS circuits responsible for arousal, perception and focus are distributed and how are susceptible to infectious, toxic, or metabolic systemic disorders. The CNS's response to such disorders is often relatively acute, and a variety of different irritants often produce the same nonspecific behavioral reactions[27].

Elderly patients with chronic diseases have an increased risk of mental state disturbance in the acute infection environment. One of the possible etiological mechanisms of encephalopathy could be due to the cytokine storm which along with other comorbidities and risk factors contributes significantly to toxic metabolic encephalopathy in severe cases[28].

Mehta et al.[29] describes a cytokine profile associated with the severity of COVID-19, characterized by an increase in interleukin (IL)-2, IL-6, IL-7, granulocyte colony stimulating factor, interferon-gamma inducible protein 10, 1-necroattract monocyte protein, 1-alpha inflammatory macrophage protein, and necrosis tumor factor. This cytokine storm in combination with different

comorbidities and metabolic imbalances could be the cause of encephalopathy.

Because COVID-19 affects more elderly and those with pre-existing conditions, patients with the previous neurological conditions and acute respiratory symptoms have an increased risk of encephalopathy at baseline[17,30]. One study reported an electroencephalogram that showed diffuse slow waves in the bilateral temporal region in the patient's studied[30].

Acute necrotizing encephalopathy (ANE)

A case of ANE hemorrhagic has also been reported in a patient diagnosed with COVID-19 who had symptoms of fever, cough, and altered mental state. Diagnosis was performed by detection of SARS-CoV-2 by PCR-TR in a nasopharyngeal sample. Brain computed tomography (CT) detected a symmetrical, bilateral hypodense area in the medial thalamic nucleus. The MRI showed hemorrhagic lesions that enhanced after contrast, multifocal and symmetrical disposition, in annular form in both thalamus, insula, and the medial region of the temporal lobes[31].

ANE is a rare complication of influenza and other infections and has been related to intracranial cytokine storms, which result in decay of the blood–brain barrier, but without direct viral invasion or parainfectious demyelination[32]. Accumulated evidence suggests that a subgroup of severe patients with COVID-19 may have cytokine storm syndrome[29].

Cerebrovascular disease

The mechanism by which SARS-CoV-2 virus enters the system by binding the S protein to ACE 2 receptors is known. ACE 2 through a signaling mechanism lowers blood pressure. Since the expression of these receptors is decreased in hypertensive patients, the ability of ACE2 to reduce blood pressure is affected in these patients. After SARS-CoV-2 infection, the expression and function of ACE2 proteins are reduced[33]. As a second line of evidence suggesting that SARS-CoV-2 infection may induce brain hemorrhage, patients with COVID-19 often suffer from coagulopathy and prolonged prothrombin time, which also contributes to secondary brain haemorrhage[33].

In addition, patients in critical condition with severe SARS-CoV-2 infections often show elevated levels of D-dimer[34] and severe reduction of platelets, which can make these patients prone to acute cerebrovascular events[15].

In a retrospective study in Wuhan, China, it was reported that 13 out of 221 COVID-19 patients developed CVD after infection; 11 (5%) developed acute ischemic stroke, 1 (0-5%) cerebral venous sinus thrombosis, and 1 (0-5%) brain hemorrhage. Patients with CVD had elderly and cardiovascular and cerebrovascular risk factors. Importantly, 11 of the 13 CVD were severe patients with SARS-CoV-2 infection, suggesting that severe infection may be an indicator of CVD, especially acute ischemic stroke. Older patients with COVID-19 may be more likely to develop CVD and more attention should be paid to older patients with cerebrovascular risk factors. Mortality was 38%[35].

The Mao et al. series describes five patients with stroke (80% ischemic), who had severe forms of COVID-19, with increased levels of D-dimer, thrombocytopenia, and multiple organ involvement[17].

Oxley et al. report the case of five patients under the age of 50, positive for COVID-19 in New York City, who suffered an ischemic cerebrovascular event[36]. Some have symptoms such as impaired consciousness, lethargy, and headache. All patients reported involvement of large brain vessels such as the internal carotid artery, the middle cerebral artery, and the posterior cerebral artery.

Anosmia, hyposmia, and dysgeusia

Although SARS-CoV-2 has many similarities to SARS-CoV and MERS, clinical data reveal differential characteristics, including olfactory alterations and hallucinations; these symptoms have not been reported in patients with SARS-CoV or MERS-CoV infection[22].

Several countries, including Germany, the United Kingdom, and Italy, have reported an increasing number of neurological manifestations such as anosmia (loss of the ability to detect one or more odors, temporary, or permanent), hyposmia (decreased sensitivity to some or all odors), ageusia (loss of taste functions), dysgeusia, or parageusia (the distortion of taste), and hypogeusia (decreased sensitivity to taste) in patients with confirmed SARS-CoV-2 infection[21].

The mechanism of neuroinvasion through the cribriform plate to the olfactory nerve, besides from being an entry mechanism to the CNS, is believed to affect the sensory capacity of the olfactory nerve. A recent study showed that nasal epithelial cells show a very high expression of ACE 2 receptors[37] within the SARS-CoV-2 infection, allowing a wide viral entry[38]. SARS-CoV has demonstrated, in a mouse model, transneuronal penetration through the olfactory bulb[14,39].

In a European multicenter study conducted by Lechien et al. 357 patients (85.6%) out of a total of 417 patients interviewed, had infection-related olfactory dysfunction. Among them, 284 (79.6%) patient had anosmia and 73 (20.4%) were hypostomatic. Fantosmia and parosmia account for 12.6% and 32.4% of patients during the course of the disease, respectively[40]. In the above-mentioned study, taste disturbances have also been reported, a total of 342 patients (88.8%) reported taste disorders, which was characterized by the deterioration of the following four flavor modalities: salty, sweet, bitter, and acidic. Taste dysfunction consisted of a reduced/discontinued or distorted capacity to identify flavors in 78.9% and 21.1% of patients, respectively[40].

The cause of dysgeusia is not yet very well established, however, in one study, a high expression of ACE 2 receptors was found in the epithelium of the tongue[41]. Animal studies show the expression of ACE 2 receptors in the solitary tract nucleus[42] which could point to the central cause of dysgeusia and a possible neuroinvasive route by continuous retrograde axonal transport in humans[43].

Periferic nervous system manifestations

Guillain-Barre syndrome (GBS)

The first case of GBS was reported, being a 61-year-old woman who had acute leg weakness and fatigue, which progressively advanced from the first day of initial symptoms. She returned from Wuhan on January 19, but denied having submitted COVID-19 compliant clinic. She was approached through a neurological examination that revealed symmetrical weakness (Medical Research Council Grade 4/5) and arreflexia in both legs and feet. Her symptoms progressed after 3 days of her admission. Muscle strength was 4/5 grade on both arms and hands and 3/5 on both legs and feet. CSF showed (5-10/L, normal: 0-8-10/L) and increased protein level (124 mg/dL, normal: 8-43 mg/dL). Nerve conduction studies (day 5) showed delayed distal latencies and absent F-waves in early course, supporting demyelinating neuropathy. On day 8 of disease evolution (January 30), the patient developed dry cough and a fever of 38.2°C. Chest CT showed ground-glass opacities in both lungs. Oropharyngeal swabs were positive for SARS-CoV-2 on RT-PCR assay. Furthermore, she was diagnosed with GBS and was given immunoglobulin intravenously[44].

It is also the case of a 76-year-old woman, transferred to the Navarra Hospital Complex for presenting a 10-day picture of the evolution of lumbar pain radiated to the back of both legs and progressive tetraparesis with distal onset paresthesias. Eight days before the beginning of the clinical manifestation, he had started with cough and fever without dyspnea, 72 h of evolution, having been treated with amoxicillin-clavulanic and azithromycin. PCR test was performed for SARS-CoV-2 detection with a positive result[45].

Even more characteristic cases of GBS have been reported, such as the report of a case of Miller Fisher syndrome and the case of a patient with multiple cranial neuropathies, both associated with COVID-19[46].

Transverse myelitis

Transverse myelitis includes a pathologically heterogeneous syndrome characterized by acute or subacute spinal dysfunction resulting in paresis, a sensory level, and an autonomic impairment (bladder, bowel, and sexual impairment) below the level of the injury[47].

A 66-year-old man with COVID-19 was admitted with acute flaccid bilateral lower extremity paralysis and urinary and intestinal incontinence. All serum microbiological test results were negative, except SARS-CoV-2 nucleic acid tests. Clinical findings indicated acute post-infectious myelitis. He was treated with ganciclovir, lopinavir/ritonavir, moxifloxacin, dexamethasone, human immunoglobulin, and mecobalamin. With a diagnosis of acute post-infectious myelitis and comprehensive treatment, bilateral lower limb paralysis improved[48].

Discussion

SARS-CoV-2 has been shown not only to be an injury to the respiratory system, affectation of different systems but has also been reported, and one of the most affected is the nervous system. The mechanisms, direct or indirect, by which many of the above manifestations are caused by COVID-19, are unknown. There is evidence of a close relationship between the onset of neurological symptoms and a history of viral infection. General symptoms such as headache or a state of confusion in a confirmed COVID-19 patient should alert the clinician, and always keep in mind the likely onset of a manifestation or eventuality that compromises the patient's prognosis.

Detection and diagnosis of COVID-19 should be rapid and accurate to reduce the rate of contagion inside and outside hospital institutions. Specialists in the area of

neurology are advised to be those patients with manifestations that guide a neurological pathology, to supplement the clinic with epidemiology in search of epidemiological links or risk factors in these patients, to establish the link between a neurological manifestation probably secondary to COVID-19. Due to the large percentage of asymptomatic patients today, it is recommended to perform current diagnostic tests such as RT-PCR, rRT-PCR, and reverse transcription loop mediated isothermal amplification[49]. Also take all biosecurity measures recommended by the Centers for Disease Control[50].

Once the diagnosis is established, Natoli et al. recommend that a record containing epidemiological data should be taken into account in patients with neurological manifestation associated with COVID-19 to fully understand whether and to what extent SARS-CoV-2 infections may cause CNS involvement. Also measure the viral load of SARS-CoV-2 in CSF in symptomatic and asymptomatic patients, for comparison. Finally, conduct research through autopsies to develop a characterization and find a distribution of the virus in different tissues, in this way, the neuropathological consequences can be determined[51].

Conclusion

SARS-CoV-2 has demonstrated great neuroinvasive ability. A neurological complication added to a disease such as COVID-19 can turn the patient's evolution and prognosis into something bleak, not to mention the possible consequences that it may leave. The mechanism by which many of the above manifestations are caused by COVID-19 is unknown, but there is evidence of a close relationship between the onset of neurological symptoms and a history of viral infection. Studies aimed at establishing physical mechanisms of these manifestations are recommended to improve both the patient's evolution and prognosis.

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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 have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Serrano-Castro PJ, Estivill-Torrús G, Cabezudo-García P, Reyes-Bueno JA, Petersen NC, Aguilar-Castillo MJ, et al. Influencia de la infección SARS-Cov2 sobre enfermedades neurodegenerativas y neuropsiquiátricas: una pandemia demorada? Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? Neurología. 2020;35:245-51.
2. Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: the most important research questions. Cell Biosci. 2020;10:40.
3. Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci. 2020;16:1678-85.
4. Palacios Cruz M, Santos E, Velázquez Cervantes MA, León Juárez M. COVID-19, a worldwide public health emergency. Rev Clin Esp. 2020;S0014-2565(20)30092-8:1-7.
5. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020;382:970-1.
6. Anderson EL, Turnham P, Griffin JR, Clarke CC. Consideration of the aerosol transmission for COVID-19 and public health. Risk Anal. 2020;40:902-7.
7. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395:514-23.
8. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA Netw Open. 2020;3:e208292.
9. Miranda-Novales MG, Vargas-Almanza I, Aragón-Nogales R. COVID-19 por SARS-CoV-2: la nueva emergencia de salud. Rev Mex Pediatr. 2019;86:213-8.
10. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res. 2020;30:367-9.
11. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87:281-6.
12. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832.
13. Cardona GC, Pájaro LD, Marzola ID, Villegas YR, Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. J Neurol Sci. 2020;412:116824.
14. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92:552–5.
15. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med. 2005;202:415-24.
16. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995-8.
17. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. MedRxiv. 2020. Disponible en: https://www.medrxiv.org/content/early/2020/02/25/2020.02.22.20026500.
18. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020 [Epub ahead of print].
19. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
20. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268-70.

21. Rodriguez-Morales AJ, Rodriguez-Morales AG, Méndez CA, Hernández-Botero S. Tracing new clinical manifestations in patients with COVID-19 in Chile and its potential relationship with the SARS-CoV-2 divergence. Curr Trop Med Rep. 2020;2020:1-4.
22. Matías-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu JA. Should we expect neurological symptoms in the SARS-CoV-2 epidemic? Neurología. 2020;35:170-5.
23. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis. 2020;94:55-8.
24. Yin R, Feng W, Wang T, Chen G, Wu T, Chen D, et al. Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. J Med Virol. 2020.
25. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun. 2020;S0889-1591(20)30465-7.
26. Carod-Artal FJ. Complicaciones neurológicas por coronavirus y COVID-19. Rev Neurol. 2020;70:311-22.
27. Krishnan V, Leung LY, Caplan LR. A neurologist's approach to delirium: diagnosis and management of toxic metabolic encephalopathies. Eur J Intern Med. 2014;25:112-6.
28. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. 2020 [Epub ahead of print].
29. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
30. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus. 2020;12:e7352.
31. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-Associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology. 2020;201187.
32. Rossi A. Imaging of acute disseminated encephalomyelitis. Neuroimaging Clin N Am. 2008;18:149-61.
33. Wang HY, Li XL, Yan ZR, Sun XP, Han J, Zhang BW. Potential neurological symptoms of COVID-19. Ther Adv Neurol Disord. 2020;13:1-2.
34. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020 [Epub ahead of print].
35. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. SSRN Electron J. 2020 [Epub ahead of print].
36. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. N Engl J Med. 2020;382:e60.
37. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020;26:681-7.
38. Marinosci A, Landis BN, Calmy A. Possible link between anosmia and COVID-19: sniffing out the truth. Eur Arch Otorhinolaryngol. 2020;77(7):2149-50.
39. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020:ciaa330.
40. Lechien JR, Chiesa-Estomba CM, de Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020:1-11.
41. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12:8.
42. Yamazato M, Ferreira AJ, Yamazato Y, Diez-Freire C, Yuan L, Gillies R, et al. Gene transfer of angiotensin-converting enzyme 2 in the nucleus tractus solitarius improves baroreceptor heart rate reflex in spontaneously hypertensive rats. J Renin Angiotensin Aldosterone Syst. 2011;12:456-61.
43. Toljan K. Letter to the editor regarding the viewpoint evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanism. ACS Chem Neurosci. 2020;11:1192-4.
44. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol. 2020;19:383-4.
45. Marta-Enguita J, Rubio-Baines I, Gastón-Zubimendi I. Síndrome de guillain-barré fatal tras infección por virus SARS-CoV2. Neurología. 2020;35:3.
46. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, et al. Miller fisher syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020 [Epub ahead of print].
47. Beh SC, Greenberg BM, Frohman T, Frohman EM. Transverse myelitis. Neurol Clin. 2013;31:79-138.
48. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. MedRxiv. 2020 [Epub ahead of print].
49. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020;55:105955.
50. Protecting Healthcare Personnel. HAI/CDC; 2020. Available from: https://www.cdc.gov/hai/prevent/ppe.html. [Last accessed on 2020 Jun 01].
51. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. Eur J Neurol. 2020 [Epub ahead of print].

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REVIEW ARTICLE

The underrated nervous system involvement by COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic virus that causes severe pneumonia and acute respiratory distress syndrome. On March 11, 2020, this novel coronavirus was declared a pandemic by the World Health Organization. To date, millions of patients have been infected. Recent reports indicate that a substantial proportion of cases present with neurological symptoms. However, it remains to be elucidated whether these manifestations are secondary to direct nervous system invasion, indirect damage mediated by a systemic inflammatory response, or a combination of both. In this review, we explore the potential routes for central nervous system involvement, the possible pathogenic mechanisms in the nervous system and the conceivable neurological long-term sequela of infection by SARS-CoV-2 infection. Future efforts should concentrate on clarifying the pathophysiology of the neurological component of COVID-19.

Key words: *COVID-19. SARS-CoV-2. Coronavirus. Neurological manifestations. Nervous system.*

Compromiso del sistema nervioso por COVID-19

Resumen

El SARS-CoV-2 es un virus altamente patogénico que causa neumonía grave y síndrome de dificultad respiratoria aguda. El 11 de marzo de 2020, este nuevo coronavirus fue declarado como pandemia por la Organización Mundial de la Salud. Hasta la fecha, millones de pacientes se han infectado. Informes recientes indican que una proporción sustancial de casos presenta síntomas neurológicos. Sin embargo, aún no se ha dilucidado si estas manifestaciones son secundarias a una invasión directa del virus al sistema nervioso, efecto del daño indirecto mediado por una respuesta inflamatoria sistémica o el resultado de una combinación de ambas situaciones. En esta revisión se describen las posibles vías para la invasión del sistema nervioso central por SARS-CoV-2 y sus mecanismos patogénicos en el sistema nervioso y las secuelas neurológicas de infección a largo plazo. Se requieren investigaciones adicionales para precisar la fisiopatología del componente neurológico del COVID-19.

Palabras clave: *COVID-19. SARS-CoV-2. Coronavirus. Sistema nervioso.*

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Introduction

The *Coronaviridae* family is comprised by enveloped positive-sense single-stranded RNA viruses, some of which are capable of causing human infection. These include several alpha-coronaviruses (human coronavirus [HCoV]-NL63 and HCoV-229E) and beta-coronaviruses (HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome-CoV [MERS-CoV], and severe acute respiratory syndrome [SARS-CoV])[1]. In December 2019, a highly pathogenic coronavirus (CoV) emerged in Wuhan, China and rapidly spread around the world[2,3]. Initially, this pathogen was named as 2019 novel CoV (2019-nCoV) by the World Health Organization. After a similar viral structure and infection pathway was discovered between this novel virus and SARS-CoV, the official name was changed to SARS-CoV-2[4,5]. The diseases caused by this nCoV are mostly related to the respiratory system and are named CoV disease 2019 (COVID-19)[5].

Even though the most widely recognized organ affected by CoVs is the respiratory system, it is important to note that CoV are not exclusively confined to the respiratory tract[6]. In fact, the neuroinvasive ability of this pathogen has been documented for almost all beta-coronaviruses in animal (mouse hepatitis virus [MHV] and porcine hemagglutinating encephalitis virus) and human (HCoV-229E, HCoV-OC43, SARS-CoV, and MERS-CoV) hosts[1,7,8]. Because of the high similarity between SARS-CoV and the novel SARS-CoV-2, it is likely that this new pathogen has analogous neuroinvasive properties. Moreover, it has been described that 36-84% of hospitalized patients with COVID-19 manifest neurological symptoms, underscoring the potential nervous system involvement by this disease[9,10]. Thus, it is important to examine the possible routes of infection by this pathogen and the neurological manifestations that patients affected by this disease might express.

Routes for nervous system involvement by SARS-CoV-2

The main mode of human-to-human transmission of the SARS-CoV-2 infection is presumed to be by respiratory droplets, which allows the virus to come into contact with mucosal epithelium (e.g., nasal mucosa) and invade susceptible cells[11]. Specifically, it has been demonstrated that this virus exhibits a high affinity to the angiotensin-converting enzyme 2, a cellular receptor that is ubiquitously expressed by respiratory epithelium, lung parenchyma, vascular endothelium renal tissue, small intestine cells, neurons and glial cells, among others[5,6].

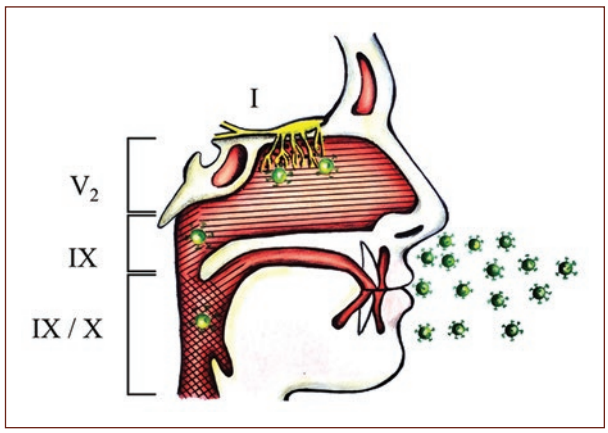

Figure 1. Potential routes of CNS invasion by SARS-CoV-2 through retrograde axonal transport from the olfactory (I), trigeminal (V), glossopharyngeal (IX), and vagus (X) cranial nerves.

Experimental models using transgenic mice have revealed that intranasal CoV inoculation could result in central nervous system (CNS) infection through retrograde axonal transport from olfactory nerves[12,13]. Hence, SARS-CoV-2 present in nasopharyngeal structures could access the brain similarly by invading local cranial nerves (i.e., olfactory, trigeminal, glossopharyngeal, and vagus nerves) (Fig. 1). Furthermore, it has been postulated that other potential pathways of invasion in patients with this disease is through the enteric nervous system or the hematogenous route[8,14]. Specifically, viremia could result in subsequent invasion of the CNS by infected leukocytes or through the endothelium of the blood–brain barrier[1]. In addition, circumventricular organs as well as dorsal root and autonomic ganglia which lack a blood-nerve barrier could act as potential hematogenous routes for pathogen entry into the CNS[15,16]. Thus, considering that multiple pathways for neurological invasion of the CNS exist, neurological manifestations of COVID-19 could be more frequent than initially presumed.

Potential mechanisms of neurological manifestations of SARS-CoV-2

A variety of neurological manifestations have been attributed to SARS-CoV-2 infection, ranging from headache to acute cerebrovascular events[17]. The mechanism of the neurological disease exhibited by COVID-19

patients might be a consequence of direct viral invasion of the nervous system, indirect CNS injury by abolition of systemic homeostasis, or a combination of both[4–6]. However, how to differentiate if a manifestation of the disease is a consequence of direct damage to the nervous system or evidence of systemic derangements is currently unclear.

Notably, the CoVs have been shown to mediate nervous system damage through virus-mediated injury to neurons and glial cells, as well as through damage mediated by the activation of the immune system[8]. On the other hand, indirect neurological manifestations can occur when there is a widespread dysregulation of homeostasis secondary to multiple organ involvement. It is now evident that SARS-CoV-2 can precipitate multiple organ failure, shock, heart failure, arrhythmias, and renal injury in addition to pneumonia and acute respiratory distress syndrome[18]. These presentations might be secondary to hypoxia, hypercoagulability, and release of excessive pro-inflammatory cytokines, which have the potential to indirectly cause neurological symptoms without CNS invasion by the virus[19,20]. Furthermore, the release of cytokines caused by viral infection could result in the permeabilization of the blood–brain barrier, allowing the invasion of the CNS by T lymphocytes and resulting in neuroinflammation[21,22]. Such disruption of the blood–brain barrier could facilitate the entry of SARS-CoV-2 through the hematogenous route, thus resulting in concurrent direct and indirect damage of the CNS mediated by this pathogen[22].

To elucidate the nervous pathophysiology of SARS-CoV-2 infection, it has been proposed that direct invasion of the CNS can be supported by the presence of viral RNA in cerebrospinal fluid (CSF). Nonetheless, failure to detect virus in the CSF does not exclude invasion of the CNS as illustrated in a case report by Paniz-Mondolfi et al.[23]. Consequently, further research is needed to determine which markers can be useful to distinguish between the direct involvement of the nervous system by SARS-CoV-2 and nervous injury secondary to systemic inflammation.

Reports of neurological manifestations in COVID-19 patients

Two large retrospective case series have examined the prevalence of neurological manifestations in patients hospitalized with COVID-19. Mao et al[9]. analyzed data from three centers located in Wuhan, China, including a total of 214 hospitalized COVID-19 patients. They found that 36.4% of their cohort exhibited neurological symptoms: 36 (16.8%) manifested dizziness, 28 (13.1%) headache, 23 (10.7%) skeletal muscle injury, 16 (7.5%) altered mental status, 12 (5.6%) hypogeusia, 11 (5.1%) hyposmia, 6 (2.8%) acute cerebrovascular disease, 5 (2.3%) neuralgia, 3 (1.4%) vision impairment, 1 (0.5%) ataxia, and 1 (0.5%) seizures. On the other hand, Helms et al[10]. reported the findings of 58 COVID-19 patients admitted to two intensive care units located in Strasbourg, France. They discovered neurological signs in 49 (84%) of their cohort: 40/58 (69%) presented agitation, 39/58 (67%) corticospinal tract signs, 26/40 (65%) confusion, 14/39 (36%) dysexecutive syndrome, and 8/49 (16%) fever > 38.5°C. Of the 13 patients that had a brain MRI because of unexplained encephalopathic features, 11/11 (100%) presented perfusion abnormalities, 8 (62%) leptomeningeal enhancement, and 3 (23%) cerebral ischemic stroke. CSF samples were analyzed for seven cases, all of which had a negative reverse transcription-polymerase chain reaction for SARS-CoV-2, which suggests that the neurologic clinical findings could have been secondary to indirect CNS injury or toxic encephalopathy.

In addition to the aforementioned studies, the study performed by Li et al[24]. merits mention as they assessed the prevalence of cerebrovascular disease in hospitalized patients with COVID-19. In 211 consecutive patients were admitted to a center in Wuhan China, 11 (5%) developed acute cerebrovascular ischemic stroke, 1 (0.5%) exhibited cerebral venous sinus thrombosis, and 1 (0.5%) presented with intracerebral hemorrhage.

Several authors have published case-series and case reports of neurological manifestations of COVID-19. These reports comprise patients aged from 24 to 79 years presenting with a variety of symptoms such as headache, altered mental status, seizures, neck rigidity, muscle weakness, incontinence, and corticospinal tract signs. The neurological diagnosis established in such cases include Guillain-Barre syndrome[25,26], encephalopathy[27,28], meningoencephalitis[2], acute myelitis[29], and intracerebral hemorrhage[30].

Noteworthy, another neurological manifestation of COVID-19 that has been proposed is neurogenic respiratory failure, which together with diffuse alveolar damage, results in difficult to treat hypoxia characteristic of severe COVID-19 cases. In particular, several authors have advocated for brain stem dysfunction caused by direct viral invasion as a possible cause for respiratory and cardiovascular derangements observed in SARS-CoV-2 infection[4,15,31].

In summary, the amount of evidence available indicates that COVID-19 is irrefutably associated with neurologic manifestations. However, to what extent these manifestations are a consequence of direct viral mediated damage has not been elucidated.

Potential long-term repercussions of COVID-19 infection

It has been previously described that CoVs have the potential to produce chronic infections in the CNS[7,8]. This can have significant clinical implications as the persistence of the viral infection could be associated with long-term neurological sequela and predispose to the development or progression of neurodegenerative and demyelinating disorders.

To date, there is no definitive evidence that links human infection by CoV to the development of chronic neurological diseases. Nonetheless, the presence of HCoV-229E and HCoV-OC43 RNA has been demonstrated in the CNS of patients with Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), and acute disseminated encephalomyelitis[8]. Particularly, the proportion of patients with detectable HCoV-OC43 RNA in brain parenchyma of patients with MS has been shown to be statistically significantly increased compared to healthy controls[32]. While it remains to be elucidated if persistent CoV infection plays a role in the pathogenesis of MS in humans, murine models have demonstrated that chronic MHV infection can induce immune-mediated demyelination[7]. Furthermore, persistence of HCoV-OC43 RNA in CNS of mice was associated with neuronal degeneration with secondary motor deficits appearing several months after acute infection by intracerebral inoculation, supporting the pathogenic role of chronic CoV infection[33].

Of note, even in the absence of chronic presence of SARS-CoV-2 in the CNS, COVID-19 infection may have long-term neurologic sequela as a consequence of microglial priming and astrogliosis. These cells might become chronically active and release pro-inflammatory cytokines even after the initial stimulus for the inflammatory response has been eliminated, possibly leading to chronic neuroinflammation even in the absence of active infection[22,31].

Consequently, as no information is currently available about the ability (of lack thereof) of SARS-CoV-2 infection to persist in CNS and mediate chronic neuronal damage, its potential to cause long-term sequela should not be dismissed.

Conclusion

Infection by SARS-CoV-2 might be associated with significant nervous involvement. However, the specific pathways for nervous system invasion and the mechanisms for neurological disease are currently unknown. As the magnitude of the acute neurological manifestations and the potential long-term repercussions of this disease are unclear, future efforts should concentrate on elucidating the pathophysiology of the neurological component of COVID-19.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Sources of funding

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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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References

1. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses. 2019;12:14.
2. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis. 2020;94:55-8.
3. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020;92:568-76.
4. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. J Med Virol. 2020;(6);552-5.
5. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020; 11:995-8.

6. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020 [Epub ahead of print].
7. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. Nat Rev Microbiol. 2006;4:121-32.
8. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res. 2014;194:145-58.
9. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;2020:e201127.
10. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268-70.
11. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med. 2020;14:126-35.
12. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82:7264-75.
13. Dubé M, Le Coupanec A, Wong AH, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. Am Soc Microbiol. 2018;92:e00404-18.
14. Pereira A. Long-term neurological threats of COVID-19: a call to update the thinking about the outcomes of the coronavirus pandemic. Front Neurol. 2020;11:308.
15. Román GC, Spencer PS, Reis J, Buguet A, El Alaoui Faris M, Katrak SM, et al. The neurology of COVID-19 revisited: a proposal from the environmental neurology specialty group of the world federation of neurology to implement international neurological registries. J Neurol Sci. 2020;414:116884.
16. Chigr F, Merzouki M, Najimi M. Comment on the neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;25960.
17. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832.
18. Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet. 2020;395:e52.
19. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020;14849.
20. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
21. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017;60:1-12.
22. Ogier M, Andéol G, Sagui E, Dal Bo G. How to detect and track chronic neurologic sequelae of covid-19? Use of auditory brainstem responses and neuroimaging for long-term patient follow-up. Brain Behav Immun Health. 2020;5:100081.
23. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;25915.
24. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. SSRN Electron J. 2020 [Epub ahead of print].
25. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Franciotta D, et al. Guillain-barré syndrome associated with SARS-CoV-2. N Engl J Med 2020 [Epub ahead of print].
26. Zhao H, Shen D, Zhou H, Liu J, Chen S. Correspondence guillain-barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol. 2020;19:P383-4.
27. Filatov A, Sharma P, Hindi F, Filatov A. Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus. 2020;12:e7930.
28. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology. 2020;201187.
29. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. MedRxiv. 2020 [Epub ahead of print].
30. Sharifi-Razavi A, Karimi N, Rouhani N. COVID 19 and intra cerebral hemorrhage: causative or coincidental. New Microbes New Infect. 2020;35:100669.
31. Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol. 2020;3:e13473.
32. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol. 2000;74:8913-21.
33. Jacomy H, Fragoso G, Almazan G, Mushynski WE, Talbot PJ. Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. Virology. 2006;349:335-46.

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REVIEW ARTICLE

Update on the management of acute stroke. A practical clinical guide

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Abstract

The diagnosis and treatment of acute ischemic stroke (AIS) have undergone great changes in the past few decades. The keys to a correct selection of the best therapeutic modality are an early identification of patients with AIS symptoms, the correct interpretation of the different neuroimaging techniques, and, if possible, to provide a reperfusion therapy as soon as possible. This review will analyze the principles of each of the new neuroimaging techniques for AIS, how these new techniques can help in clinical practice, the different treatment options, as well as the inclusion and exclusion criteria for each of them. A systematic research was conducted on MEDLINE (PubMed), using the following Medical Subject Headings terms: (AIS) + (neuroimaging/techniques) + (thrombolytic therapy) + (mechanical thrombectomy). We selected original articles, as well as clinical trials and review articles. Each article was read to completion, to check for other useful references. We also reviewed the different therapeutic options for AIS, including endovascular approaches through a selection of the most recent neuroimaging techniques. In conclusion, intravenous thrombolysis continues to be the cornerstone for the treatment of AIS. The attending physician has a fundamental role in suspecting and confirming large vessel occlusions, and in deciding which is the most appropriate therapeutic option for each case, with important prognostic implications for the patient.

Key words: *Stroke. Acute ischemic stroke. Thrombolysis. Mechanical thrombectomy.*

Actualización sobre el manejo del infarto cerebral agudo. Guía clínica práctica

Resumen

El diagnóstico y tratamiento del infarto cerebral agudo (ICA) han sufrido grandes modificaciones en las últimas décadas. Las claves para la correcta selección de la mejor modalidad terapéutica son la identificación temprana de pacientes con datos de ICA, la correcta interpretación de las diferentes técnicas de neuroimagen y el proveer una terapia de reperfusión tan pronto como sea posible. Esta revisión analizará los principios de las distintas técnicas de neuroimagen en el ICA, la aplicación de estas nuevas técnicas en la práctica clínica, las diferentes opciones de tratamiento, y los criterios de inclusión/exclusión para cada uno de ellos. Se realizó una búsqueda sistemática de la literatura en MEDLINE (Pubmed), unificando los criterios de búsqueda mediante términos MeSH [infarto cerebral agudo] + [neuroimagen/métodos] + [terapia trombolítica] + [trombectomía mecánica]. Se llevó a cabo una selección de los estudios originales, así como de los ensayos clínicos,

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incluyendo artículos de revisión. Cada artículo fue revisado en su totalidad en busqueda de otras referencias que pudieran ser aportadas por cada artículo. Posteriormente, se desarrolló una revisión de las opciones terapéuticas actuales de reperfusión en el ICA, incluyendo el manejo endovascular mediante la selección de nuevas técnicas de neuroimagen. En conclusión, la piedra angular del tratamiento del ICA continúa siendo la trombólisis intravenosa. El médico tratante tiene un papel fundamental en la sospecha y confirmación de oclusión de gran vaso y en la selección de las diferentes modalidades terapéuticas, todo esto con importantes implicaciones pronósticas para el paciente.

Palabras clave: *Infarto cerebral. EVC. EVC agudo. Trombólisis. Trombectomía mecánica.*

Introduction

Worldwide, stroke is responsible for approximately 5.5 million deaths and 116 disability-adjusted life years[1]. The estimated incidence of this disease will keep on increasing, in part due to the ever-expanding population with metabolic disease. Until 2015, the only acute treatment available to patients with acute stroke was intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA), and only when it could be administered in the first 4.5 h from symptom onset[2]. Over the past few years, new therapies for acute ischemic stroke (AIS) have had a major impact on the functional outcome and survival of stroke patients[2]. AIS caused by large vessel occlusion (LVO), which 10 years ago had a somber prognosis, is today an important therapeutic target of interventional vascular neurology[3]. LVO ischemic strokes are more likely to have a poor functional outcome when compared to those occurring due to distal occlusion and are responsible for up to 90% of the mortality and 60% of dependence in patients with ischemic stroke[4,5].

In 2015, based on the evidence of five clinical trials, the American Heart Association/American Stroke Association (AHA/ASA) included mechanical thrombectomy (MT) within 6 h of symptom onset as a therapy with level IA evidence, for patients with AIS due to a LVO[6]. After several trials showed that this therapy could be used for selected patients in even longer time windows, the 2019 update of these guidelines adopted an extended therapeutic window[7]. MT requires a selection of patients based on clinical and imaging criteria, including the need for vessel imaging with computed tomography angiography (CTA) or magnetic resonance angiography (MRA) in the 6-h window and an evaluation of mismatch between the stroke core and the area of tissue at risk using magnetic resonance imaging (MRI), computed tomography perfusion (CTP) and/or perfusion-weighted imaging MRI (Magnetic resonance perfusion [MRP])[8,9].

Despite their important impact on AIS outcome, rtPA and MT are only available in two thirds of countries worldwide, but are underused in low- and middle-income countries[10]. To effectively employ these new therapies, healthcare systems must implement policies to ensure access to diagnostic and therapeutic interventions for patients with AIS. In Mexico, few of these processes have been implemented, and there are significant delays in accessing such health system and few hospitals have the necessary processes to deploy these new treatment modalities, although the use of rtPA has increased since 2005[11,12]. In a recent study done at four Mexican hospitals with AIS protocols that included data from 500 patients, the time from symptom onset to arrival at the hospital was approximately 11 h; for 7.6% of patients who were treated with rtPA, the door-to-needle time was 82 ± 51 min. The proportion of patients who lived independently 6 months later was 68.4% among those treated with rtPA and 41.7% in those not treated[11].

Here, we review the principles of neuroimaging, how to interpret data and summarize the imaging criteria for AIS treatment. We also discuss how the new techniques can help in clinical practice, the different treatment options, as well as the inclusion and exclusion criteria for each of them, according to the available evidence.

This article was created through a systematic qualitative search in DATABASES, PUBMED, MEDLINE, LILACS, and EMBASE using the following Medical Subject Headings terms: (AIS) + (neuroinmaging/techniques) + (thrombolytic therapy) + (MT). Then, we selected the main papers and trials regarding the current treatment and selection criteria for the management of AIS, as well as the most recent and used criteria for the different neuroimaging modalities. All papers were required to have been published in a good quality journal with a good impact factor. The most widely used guidelines were added and reviewed. Finally, our team discussed all the information that was included, with the senior researcher (AA) having the final word on any disagreements among the junior researchers.

What are the important concepts related to AIS imaging?

The aim of the most novel neuroimaging techniques in the context of acute cerebral ischemia is to distinguish likely infarcted and unsalvageable areas of the brain (ischemic core) from potentially salvageable tissue (penumbra). The ischemic core is key to determine the outcome. It is time-sensitive and could be assessed using diffusion-weighted imaging (DWI) or CTP. Penumbra is the target of reperfusion therapy and, while it is not a novel concept, it is now measured with neuroimaging techniques. Perfusion imaging has helped proof-of-concept studies, and reperfusion has been observed to correlate with a better clinical outcome in patients with a considerable amount of tissue at risk of infarction. Below, we review the most important concepts in the AIS treatment and its correlation with neuroimaging[13].

Cerebral blood flow (CBF)

- CBF is defined as the blood volume that flows per unit mass per unit time in brain tissue and is typically expressed in units of $ml_{blood}/100\ g_{tissue}/min$[14]. When discussing neuroimaging studies, CBF has a very similar definition, with the tissue being represented as a voxel[15].
- Normal: 60-100 ml/100 g/min
- Hypoperfusion refers to CBF < 60 ml/100 g/min. When CBF ranges from 22 to 60 ml/100 g/min, the tissue is considered oligemic and may or may not spontaneously recover without reperfusion therapy, and thus vigilance is warranted. Ischemia develops when CBF < 22 ml/100 g/min. If reperfusion is re-established quickly, the tissue may recover; otherwise, it will die. Hypoperfusion is further classified in the following:
  - Oligemia: asymptomatic hypoperfusion with spontaneous recovery and no need for reperfusion therapy. CBF is 22-60 ml/100 g/min.
  - Ischemia: symptomatic hypoperfusion that may or may not respond to reperfusion therapies, depending on stroke severity. CBF is < 22 ml/100 g/min.
  - Penumbra: the tissue surrounding the ischemic core, and by definition, can recover from ischemia. Penumbra may be sustained by collateral circulation, and the time it will remain viable will differ from patient to patient. This condition warrants reperfusion therapy. CBF is 22-10 ml/100 g/min.
  - Ischemic core: dead, non-recoverable tissue. CBF is < 10 ml/100 g/min[14].

The mismatch may have different meanings, depending on the imaging method; it is used differently when talking about perfusion imaging, MRI, and the relationship between symptoms and imaging. Mainly, it is used to describe the presence of salvageable tissue. Several studies (EPITHET[16], DEFUSE[17], and DEFUSE-2[18]) have shown an association between the degree of reperfusion and clinical outcomes in patients with mismatch; this confirms that reperfusion relates to better clinical outcomes in patients with mismatch. A mismatch can be defined according to the study with which it is assessed.

- CTP mismatch: we talk about a mismatch when there is a difference in the volume of the area with a severe cerebral blood volume (CBV) decrease and delayed CBF; it is a way to operationalize the concept of ischemic core and penumbra[19].
- DWI-perfusion weighted imaging (DWI-PWI) MRI mismatch: the mismatch between these two imaging modalities is thought to be a hallmark of ischemic penumbra[19] and can be used to estimate the extent of the penumbra[20]. Some of the DWI lesion is potentially reversible, and some of the peripheral regions of the perfusion abnormality will not progress to infarction, and thus may benefit from intravenous thrombolysis[20].
- Fluid attenuation inversion recovery-DWI (FLAIR-DWI) MRI mismatch: related to the differences in DWI and FLAIR or T2 sequence; ischemic injuries will appear at different times in each of the previously mentioned sequences: DWI will show hyperintensities in the 1st few min of a stroke, while FLAIR will manifest hyperintensities (in the same regions as DWI) from 6 h onward. A mismatch in this context refers to DWI that shows hyperintensities, but FLAIR and/or T2 has no such changes, which suggests that the lesion is acute, and thus may warrant reperfusion therapy. On the other hand, if the same hyperintensity appears both in DWI and FLAIR, there is no mismatch, which means that the ischemic injury is already established, and thus, this tissue is not salvageable[21].
- Clinical-radiological mismatch refers to patients that may present with clinical features that do not seem to correlate to the neuroimaging findings (severe deficit and mild imaging features, and vice versa). Such is the case with posterior circulation injuries, in which small lesions may cause a very striking clinical picture; this is because structures in the posterior fossa and brainstem are very small and tend to be packed together[9].

Vessel occlusion

In imaging studies with an angiographical sequence, an occlusion can be appreciated as an amputation, interruption, or reduction in vessel continuity or width. CTA and MRA identify LVOs involving the internal carotid artery (ICA), middle cerebral artery (MCA), and anterior cerebral artery (ACA) in the anterior circulation, and the basilar and vertebral arteries in the posterior circulation. By location, the LVO can be classified as[22]:

- Proximal occlusion: the occlusion is at the level of the first portion of ACA, MCA, and the final portion of the ICA.
- Distal occlusion: the occlusion is beyond the established limits for a proximal occlusion, or in vessels other than those mentioned for proximal occlusion.

LVOs can be identified with a neuroimaging study of the intracranial vessels. Because of their availability and diagnostic precision, CTA is usually the preferred method, and it should include the supra-aortic vessels. In the acute period (< 24 h), patients with a confirmed National Institutes of Health Stroke Scale (NIHSS) > 6 may warrant neuroimaging with angiography to determine the level of the occlusion[23], depending on the patient's characteristics.

Clinical severity

The most widely used tool to clinically quantify AIS severity is the NIHSS, in which a higher score means greater stroke severity[24]. While the definition of minor stroke has changed over time, the accepted definition by the AHA/ASA guidelines is NIHSS < 5[7].

According to a trial that analyzed various clinical scales for AIS, a NIHSS ≥ 11 may yield good accuracy (79%) and for LVO diagnosis, with the drawback of 27% false negatives. NIHSS ≥ 6 has a greater sensibility (87%) for LVO diagnosis, at the expense of 40% false positives and an accuracy of 69%[25].

Which are the imaging methods to evaluate AIS patients?

The timely detection of an AIS, and correct identification of candidates for rtPA or MT (or a combination of both), depends on clinical and neuroimaging findings. The different neuroimaging methods depend on the availability in each center, and all the techniques are useful to predict which patients with AIS will benefit from acute treatment, and which ones have a higher risk of hemorrhagic complications. The time criterion is still the most widely used marker for patient selection for reperfusion therapies, especially for rtPA[7].

Nowadays, neuroimaging protocols are being developed to optimize patient selection, with a renewed interest in perfusion studies. In this line of thought, some trials have begun to focus on collaterals, which may be a valuable biomarker in the future[9]. Ideally, in neuroimaging studies, we should evaluate the parenchyma, cerebral vessels, cerebral perfusion, ischemic core, and penumbra. Although there are multiple imaging techniques for patient selection, a non-contrast computed tomography (NCCT) may be sufficient for the management with rtPA, which remains the standard treatment[7].

NCCT

NCCT alone is used in the initial assessment of patients with the clinical diagnosis of AIS. NCCT has three uses in the acute period: ruling out hemorrhage, detection of non-acute lesions, and detecting hyperacute changes that may suggest acute ischemia. In most stroke centers, the first study in the evaluation of suspected AIS is a NCCT, as it answers the first question one should ask themselves when dealing with an acute, sudden neurological deficit: "does this patient have an intracranial hemorrhage?"[9] If no bleeding is detected, and, depending on clinical variables, rtPA could be initiated if inclusion criteria were met. The classic early ischemic signs seen in NCCT (Fig. 1) are obscuration of the lentiform nucleus, loss of gray-white matter differentiation at the insula (insular ribbon sign), loss of gray-white matter differentiation at the surface cortex, and hyperdense artery sing (may be indicative of a thrombus within the MCA)[22]. The Alberta Stroke Program Early CT Score (ASPECTS, Fig. 2)[26] is the most widely used method to assess the extent of early ischemic changes[27]. ASPECTS is a validated, prospective score, that allows us to have an idea of the infarct's extension. This method divides the MCA's territory into ten regions, and for each hypodensity, in each of these regions we will subtract a point (the abnormality must appear on at least two consecutive 5 mm cuts); a score of < 6 is considered to suggest extensive, established injury, and a lower probability of a good outcome[27]. In general, an ASPECTS of 6-10 was used as an inclusion criterion in endovascular trials, such as ESCAPE[28], SWIFT PRIME[29], and REVASCAT[30], to select patients with a relatively small core infarct. ASPECTS assessment is affected by CT quality. It is important for the grayscale of NCCT to be properly adjusted for brain parenchyma

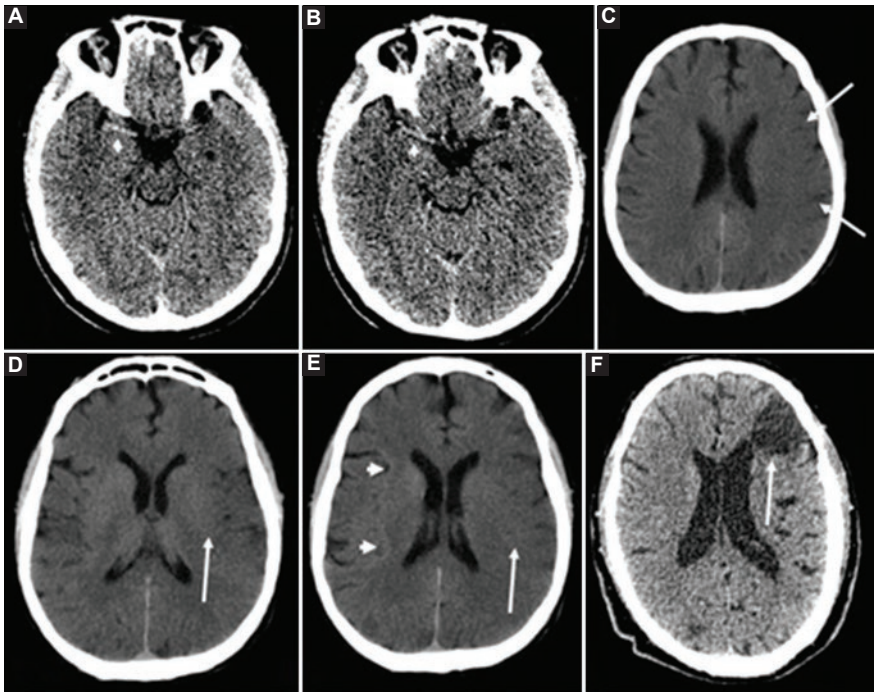

Figure 1. Classic early ischemic signs in a non-contrast computed tomography: **A and B:** show a hyperdense right middle cerebral artery sign (white arrow head). **C:** shows the loss of gray-white matter differentiation at the surface cortex (white arrows). **D:** hypoattenuation of the lentiform nucleus (white arrow). **E:** loss of gray-white matter differentiation at the left insula (insular ribbon sign, white arrow) compared to a normal right insular ribbon (white arrowheads). **F:** shows a chronic cortical infarct (white arrow) with ventricular deforming due to gliosis.

so that the gray-white matter differentiation is readily distinguished[9].

NCCT is considered suboptimal to evaluate the posterior fossa due to artifacts caused by bony structures. Since it is the most basic study for AIS, it does not allow us to evaluate other relevant variables, such as the site of occlusion or collaterals[22]. Still, there may be times when the clinician will have to evaluate the posterior fossa with only a NCCT, and it is for these situations that pc-ASPECTS[31] was developed; it is used in the same manner as ASPECTS and accounts for the territories supplied by the vertebrobasilar system. As of now, it has not seen much use in the clinical field.

NCCT is also useful to discard any stroke mimics that could otherwise lead to unnecessary reperfusion therapy. Mimics are non-stroke disorders with a presentation that could suggest AIS, such as an intracranial hemorrhage or tumors[32].

CTA

The primary modality used to assess blood vessels is CTA, which is increasingly used as part of the initial imaging protocol to identify patients with LVO. CTA is also the most frequently used vascular imaging modality in clinical trials and clinical practice. This sequence can be obtained on all modern CT scanners and can be easily incorporated into an AIS imaging protocol. It requires intravenous iodinated contrast and, depending on the equipment that is used, is usually completed within 2 min. There may be concern for the use of contrast, but the 2019 update to the AHA guidelines states that the risk of contrast-induced nephropathy is relatively low, and waiting for the laboratory results may delay treatment; this is especially true in patients with no known history of kidney disease[7], and even then, according to a systematic review, neither CTA nor CTP increase the risk of acute kidney injury in patients with known chronic kidney disease[33]. CTA allows us to pinpoint the location, extension of the vessel occlusion, and identifying thrombi in large proximal intracranial arteries. Determining the location of the thrombus helps predict the likelihood that thrombus will respond to rtPA or MT, especially in tandem lesions (occlusions with both intracranial and extracranial components)[34]. An LVO will appear as an amputation (Fig. 3) or reduction

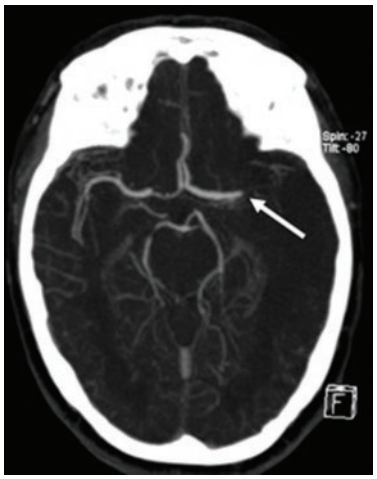

Figure 2. Middle cerebral artery territories according to ASPECTS in a NCCT. Caudate nucleus (C), insular ribbon (I), posterior arm of the internal capsule (IC), lenticular nucleus (L), anterior MCA cortex (M1), MCA cortex lateral to the insular ribbon (M2), posterior MCA cortex (M3), superior-anterior MCA cortex (ACA-MCA watershed territory; M4), frontal posterior MCA cortex (M5), parietal cortex (M6). It is necessary to have at least one cut at the level of the basal ganglia and thalamus and another one just above the basal ganglia. ACA: anterior cerebral artery; ASPECTS: Alberta stroke program early CT score; MCA: middle cerebral artery; NCCT: non-contrast computed tomography.

of the affected vessel's caliber. It is also possible to measure thrombus length, which will influence recanalization potential, which is to say that clot length has been reported to be inversely proportional to rtPA effectiveness, especially if said clot is > 8 mm[35]. This is not normally used in the clinical setting and is currently not included in any guidelines.

CTA also allows us to qualify collaterals using a less standardized scale than the one used for digital subtraction angiography (DSA), characterizing findings as: robust collaterals (collateral circulation is symmetric between the affected and the healthy hemispheres); intermediate collaterals (collateral circulation is appreciated in 50-99% of the tissue at risk); poor collaterals (30-50% in the tissue at risk). Patients with better collaterals seem to not only fare better but also appear to have a lower bleeding risk by reperfusion injury[36]. As of now, this information is still under research, there are no standardized CTA scales for collaterals, and collateral grading is not used in guidelines, so it is not a parameter to exclude patients from reperfusion therapy.

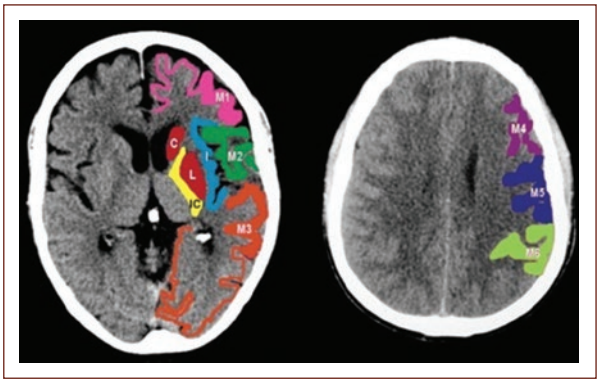

Figure 3. Computed tomography angiography with occlusion of the left middle cerebral artery (white arrow).

CTA is also useful to determine the etiology of an ischemic stroke and to identify underlying pathologies, such as carotid atherosclerosis (artery-to-artery embolism), intracranial atherosclerosis, or arterial dissection[22]. Figure 3 shows a CTA with occlusion of the left MCA.

Computed tomography (CT) perfusion

Perfusion imaging, using either CT or MRI, has been used to select patients for treatment outside the recommended time window. Perfusion studies use contrast to measure the amount and time it takes for intravenous contrast to pass through certain areas of the brain and can help identify the ischemic core and penumbra. Recent studies (DAWN[37] and DEFUSE 3[38]) showed improved outcomes after MT for patients selected by specific parameters or perfusion. Its primary role in AIS is determining whether brain tissue is hypoperfused and, therefore, at risk of infarction. Penumbra (viable tissue) is the target for reperfusion therapy. CTP can be performed in a few minutes and gives us a number of measures, especially CBF and CBV. During acquisition for a CTP, the brain is repeatedly scanned during the passing of intravenous contrast throughout the brain parenchyma. As the contrast flows, the relative increase, peak, and the decrease in radiodensity create an attenuation-time curve. These curves are calculated for an arterial and venous input function and outflow, allowing to measure perfusion for each voxel. Unlike multiphase CTA, CTP involves acquiring many such images, which results in a higher radiation dose than CTA. This repeated scanning of the brain allows the generation of estimates for CBF, blood volume, median transit time, time to peak (TTP), time

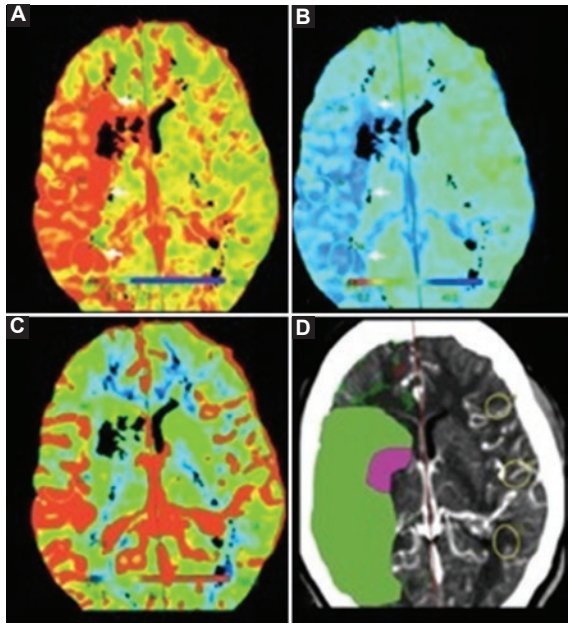

Figure 4. CTP with mismatch due to a large region of ischemic penumbra (salvageable hypoperfused tissue), compared to the ischemic core (unsalvageable tissue). **A:** CBF map shows a region of decreased perfusion within the right MCA territory (white arrowheads). **B:** median transit time map shows an increased blood contrast time that matches the same region as (white arrowheads). **C:** CBV map demonstrates no abnormality. **D:** large ischemic penumbra (green) with a small ischemic core (purple), representing a CTP mismatch. CBF: cerebral blood flow; CBV: cerebral blood volume; CTP: computed tomography perfusion; MCA: middle cerebral artery; MTT: median transit time.

to drain, and tissue permeability. These measurements are shown in color-coded parametric maps, representing each variable. The ischemic core is identified by markedly reduced CBF and reduced CBV, with a marked delay in TTP and mean transit time. By contrast, the ischemic penumbra, which usually surrounds the ischemic core, has prolonged mean transit time but has only moderately reduced CBF and near-normal or even increased CBV (Fig. 4)[17]. It is now established that its use does not delay rtPA application, nor intervention through MT when compared to NCCT[39], and it is associated with more reperfusion therapy use[40]. A systematic review of AIS diagnosis with CTP showed high sensitivity (80-82%) and very high specificity (95%). Its limitation in AIS includes that it can miss lacunar infarcts and has a relatively low sensitivity for posterior circulation infarcts[41]. CTP may also cause significant delays in workflow due to the longer acquisition and processing times and does not invariably provide accurate information. Several studies have shown that automated processing of CTP can provide a quantitative mismatch classification. Recently, DAWN[37] and DEFUSE 3[38] used automated software (RAPID) to determine the ischemic core and showed excellent clinical outcomes in patients treated up to 24 h from symptom onset.

MRI

MRI can provide estimates of penumbral tissue through the combination of diffusion and perfusion imaging, but in practice, this is less available and more difficult to interpret. MRI sequences considered to be essential for AIS are apparent diffusion coefficient (ADC), DWI (ischemic findings appear from the 1st few min after symptom onset), susceptibility-weighted imaging (SWI, so as to detect any hemorrhage that may not be evident in other sequences), and FLAIR (ischemic changes will appear after 6 h from symptom onset). ADC is used in conjunction with DWI to distinguish truly ischemic lesions. DWI is highly sensible (88-100%), specific (95-100%), and accurate (95%) to detect and delimitate parenchyma at risk of infarction[9]. This sequence can demonstrate hyperintensities in oligemic tissue and may overestimate infarct size[13], so information obtained with his method must be interpreted with caution. Lesion volume determined by DWI and its pattern seems to be related to collateral flow grade in AIS[42]. Supratentorial infarcts with a great volume (> 100 ml) are related to higher bleeding risk and lower possibilities of benefit from MT; those of intermediate size (70 - 100 ml) have an uncertain prognosis regarding reperfusion therapy[43]. MRI is more useful than NCCT to evaluate the posterior fossa and brainstem, as MRI presents no bone artifact. Both NCCT and MRI have distinct and clearly defined roles in decision-making. Figure 5A and B shows a DWI-FLAIR mismatch, while figure 5C-D shows no mismatch.

MRA

MRA is useful when a patient in whom LVO is suspected and cannot receive iodinated contrast for CTA. The main limitation lies in that MRA may overestimate the degree of stenosis and may be inaccurate to detect a distal occlusion, as MRI is dependent on flow and does not adequately represent intraluminal anatomy, unlike CTA[9].

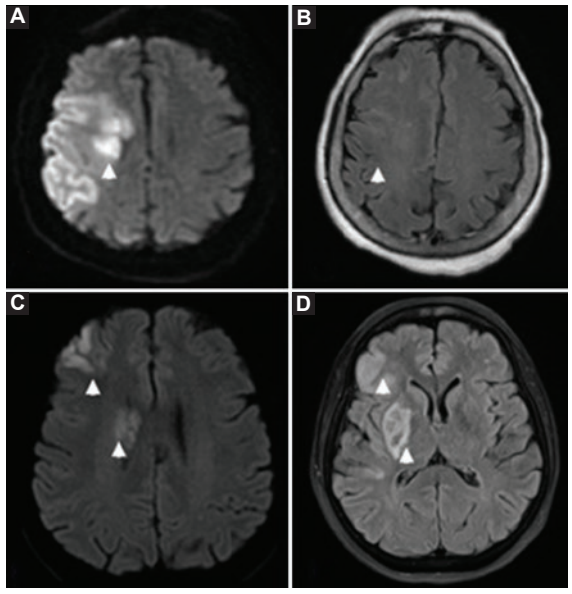

Figure 5. Magnetic resonance imaging in patients with acute ischemic stroke. Lesion shown on diffusion-weighted imaging (DWI) **(A)** but not on fluid attenuation inversion recovery (FLAIR) imaging **(B)**; thus, it is considered a DWI-FLAIR mismatch. Meanwhile, the lesion on DWI **(C)** has a corresponding parenchymal hyperintensity on FLAIR **(D)**, so there is no mismatch.

Table 1. Reperfusion of large vessel occlusion (LVO) defined by modified Thrombolysis in Cerebral Ischemia (mTICI)

Grade	Definitions
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, with limited distal branch filling with little or slow distal reperfusion
2a	Antegrade reperfusion of less than half of the ischemic territory
2b	Antegrade reperfusion of more than half of the ischemic territory
3	Complete antegrade reperfusion, with no occlusion at the distal branches

Table 2. American Society of Interventional and Therapeutic Neuroradiology/Society of interventional Radiology (ASITN/SIR) collateral grade scale

Grade	Angiographic collaterals (Digital subtraction angiography)
0	No collaterals visible at the ischemic region
1	Slow collaterals to the periphery of the ischemic region with the persistence of some of the defect
2	Rapid collaterals to the periphery of the ischemic region, with the persistence of some of the defect and to only a portion of the ischemic territory
3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

MR

MRP can create similar maps as CTP, so findings and definitions are the same for both studies. The role of this modality is still debated. MRP has the advantage of not using ionizing radiation, unlike CTP[9]. MRP can opt-out of using contrast with arterial spin labeling, a sequence with the capacity of proving flow information, with the drawback of not providing volume measures, so penumbra cannot be delimited. It is mostly used to study tumoral lesions[22,44].

DSA

DSA is considered the gold standard to evaluate vessel morphology, level, and occlusion percentage. The thrombolysis in cerebral infarction (TICI) scale was developed for DSA studies with the objective of quantifying response to reperfusion therapies[45]; nowadays, a modified version (mTICI, Table 1) is used, which reflects the increasing use of MT[46]. DSA also allows us to evaluate collaterals using the American Society of Interventional and Therapeutic Neuroradiology/Society of interventional Radiology scale (Table 2), which is useful to characterize collaterals quality, with very important implications for clinical outcome[47]. The use of DSA (outside MT) in AIS is decreasing, although it is still used when in doubt, even after CTA or MRA[43]. Figure 6 shows a DSA before and after the retrieval of a thrombus that was occluding the proximal right MCA.

What are the current therapies and how to select patients for each of them?

Clinical decisions for treatment in acute stroke include a brief history and examination followed by imaging, leading to quick action (Fig. 7). Clinical evaluation based on NIHSS is the first step inpatient

Table 3. Inclusion and exclusion criteria for the treatment of acute ischemic stroke with alteplase, with additional warnings for the extended therapeutic window

Inclusion criteria
- Clinical diagnosis of IS causing the measurable neurologic deficit
- Onset of symptoms < 4.5 h before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal or at neurologic baseline
- Age ≥ 18 years

Exclusion criteria
- IS or severe head trauma in the previous 3 months
- Previous ICH
- Intra-axial intracranial neoplasm
- Gastrointestinal malignancy or hemorrhage in the previous 21 days
- Intracranial or intraspinal surgery within the prior 3 months
- Symptoms suggestive of SAH
- Persistent BP elevation (systolic ≥ 185 mmHg or diastolic ≥ 110 mmHg)
- Active internal bleeding
- Presentation consistent with infective endocarditis
- Stroke known or suspected to be associated with aortic arch dissection
- Acute bleeding diathesis
- Platelet count < 100,000/mm^3
- Current anticoagulant use with an INR > 1.7 or PT > 15 s or aPTT > 40 s or PT > 15 s
- Therapeutic doses of LMWH within 24 h (e.g., to treat VTE and ACS); this exclusion does not apply to prophylactic doses
- Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests such as aPTT, INR, ECT, TT, or appropriate factor Xa activity assays
- Head CT: evidence of hemorrhage, or extensive regions of obvious hypodensity suggestive or irreversible injury

Warnings
- Only minor and isolated neurologic signs or rapidly improving symptoms
- Serum glucose < 50 mg/dL (< 2.8 mmol/L)
- Serious trauma in the previous 14 days
- Major surgery in the previous 14 days
- History of gastrointestinal bleeding (remote) or genitourinary bleeding
- Seizure at the onset of stroke with postictal neurologic impairments
- Pregnancy
- Arterial puncture at a non-compressible site in the previous 7 days
- Large (≥ 10 mm), untreated, unruptured intracranial aneurysm
- Untreated intracranial vascular malformation

Additional warnings for treatment from 3 to 4.5 h from symptom onset
- Age > 80 years
- Oral anticoagulant use regardless of INR
- Severe stroke (NIHSS score > 25)
- Combination of both previous ischemic stroke and diabetes mellitus

ACS: acute coronary syndrome; aPTT: activated partial thromboplastin time; ECT: ecarin clotting time; INR: international normalized ratio; PT: prothrombin time; NIHSS: National Institutes of Health Stroke Scale; tPA: intravenous alteplase; TT: thrombin time; VTE: venous thromboembolism; ISL: ischemic stroke; ICH: intracranial hemorrhage; SBP: systolic blood pressure; SAH: subaracnoid hemorrhage; LMWH: low molecular weight heparin; BP: blood pressure.

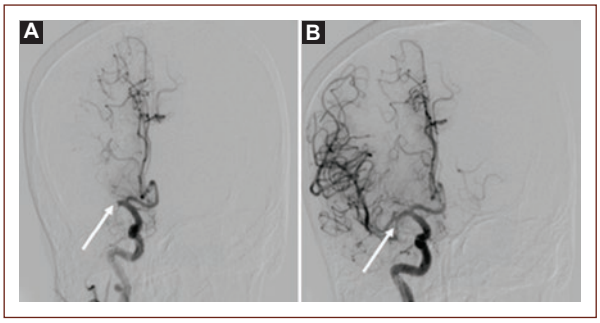

Figure 6. Posteroanterior digital subtraction angiography before **(A)** and after **(B)** thrombectomy for a right middle cerebral artery occlusion.

evaluation. It is clear, according to different studies, that there is a correlation between the NIHSS score and outcome[48]. Seminal MT trials DAWN[35] and DEFUSE 3[36] included patients with a median NIHSS of 16-17 points, and DEFUSE 3[38] included patients with a mean ASPECTS of 8, which implies that in extended therapeutic windows, patients with severe stroke could be excluded.

Current reperfusion therapies are rtPA and MT, or a combination of both of them. rtPA is the first-line treatment for AIS, as long as it can be administered in < 4.5 h from symptom onset, and no exclusion criteria are met (Table 3); it is within this timeframe that mismatch criteria are not needed, and the only advanced neurimaging technique that could be used is CTA, if the patient were suspected to be a candidate for MT. These first 4.5 h are divided into a classical window (0-3 h after symptom onset) and an extended window (3-4.5 h); the latter has some specific criteria that must be met before initiating rtPA[7]. It must be stressed that some of the criteria that were previously considered to be contraindications for rtPA (age > 80 years-old, NIHSS > 25, previous stroke in a diabetic patient, etc.) are now considered merely warnings for rtPA during the extended window and are in no way a reason for the physician to refrain from administering rtPA[7].

The recanalization rate for patients with a distal occlusion who are treated with rtPA goes from 38% to 50%[49,50]. rtPA is a drug with a number of benefits that

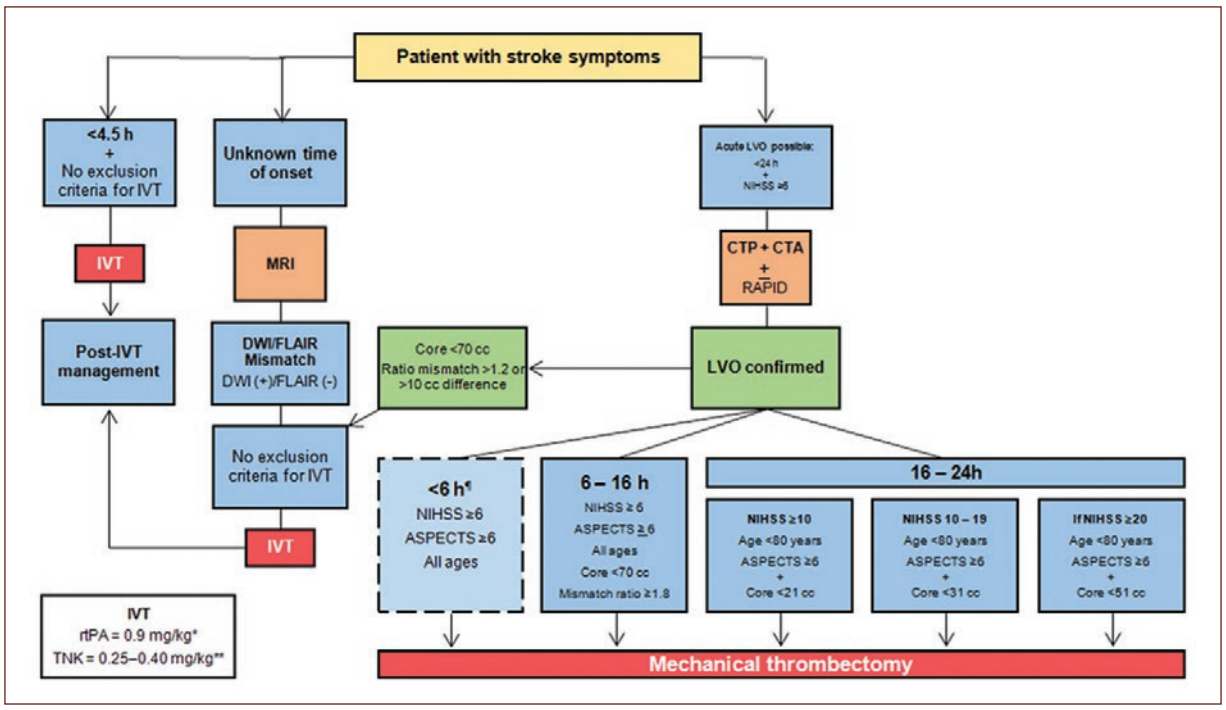

Figure 7. Treatment algorithm in acute ischemic stroke. CTA: computed tomography angiography; CTP: computed tomography perfusion; DWI: diffusion-weighted imaging; FLAIR: fluid attenuation inversion recovery; IVT: intravenous thrombolysis; LVO: large vessel occlusion; MRI: magnetic resonance imaging; NIHSS: National Institutes of Health Stroke Scale; RAPID is an automated software for CTP; rtPA: recombinant tissue plasminogen activator; TNK: tenecteplase; w/o: without. No brain perfusion imaging needed before 6 h for thrombectomy. *Maximum dose: 90 mg. **Depending if the patient will receive MT. Maximum dose: 25 mg.

depend on the speediness with which it is applied. It is estimated that for every 30 min of treatment delay, chances of a good clinical outcome decrease by 10-15%[51]. The therapeutic windows are determined by the time from symptom onset. Inclusion and exclusion criteria, as well as additional warnings for rtPA have not been modified since 2008. rtPA is the most used drug for intravenous thrombolysis, although there is a growing body of evidence that supports tenecteplase (TNK) as either and safe alternative or even as a potential replacement for rtPA. rtPA binds to the fibrin in a thrombus and causes the plasminogen within the clot to convert to plasmin, which will break down the thrombus[46].

Candidates for MT must receive rtPA as soon as possible. The treating physician must keep in mind that MT is not a contraindication for rtPA and that under no circumstances, one should wait for rtPA response in a patient with LVO to decide if they should be taken to MT[23]. During MT, every time a device is directed at the thrombus with the objective or removing it, it is called a "pass." With second-generation devices, MT may achieve a complete or near-complete (TICI 2B/3) recanalization rate of up to 84%[52]. In a trial that included 330 patients, the investigators tried to determine which was the minimal necessary number of attempt for MT; there was a median of 1 pass, with an achieved TICI 2B or 3 in 46.8% of patients; after three passes, the goal was met in 67.9%. Better clinical outcomes were observed in those with 1-3 passes[53].

After 4.5 h of symptom onset, the only treatment option is MT. Although the therapeutic window has extended up to 24 h, the more time passes, the selection of patients becomes more rigorous and requires more elements to demonstrate viable brain tissue[7,35]. The criteria on which treatments are based beyond 6 h of evolution, wake-up stroke, minor stroke, and in some specific situations are described below.

Thrombolysis in minor stroke

Minor stroke is one of the most commonly cited reasons for nonuse of rtPA within the classical and

extended time windows, and benefits regarding reperfusion therapy with rtPA in this context remains unclear. Prospective data suggest that 30% of patients with a minor stroke will have a functional disability (modified Rankin Scale [mRS] > 2) at 90 days after stroke[54]. The most recent recommendations establish that for patients with mild but disabling stroke symptoms (NIHSS 0-5 that prevents the patient from performing basic daily activities or returning to work)[54], rtPA should be administered within 3 h from symptoms onset or from last known well (Strength of recommendation Class I, Level of Evidence B) and its use may be reasonable in the group of patients within the extended window (Strength of recommendation Class IIb, Level of evidence B)[7].

Thrombolysis and anticoagulation

Some patients, particularly those with known non-valvular atrial fibrillation (NVAF), are treated with direct oral anticoagulants. Even with these drugs, approximately 1-2% of these patients will have a stroke[55]. Active anticoagulation for patients with NVAF can be achieved with either vitamin K-dependent (e.g., acenocumarin), or with direct oral anticoagulants (factor Xa inhibitors such as apixaban or rivaroxaban, and direct thrombin inhibitors, e.g., dabigatran) is a contraindication for rtPA (Table 3). Factor Xa inhibitors and direct thrombin inhibitors have an additional warning if the last intake was within 48 h from symptom onset, or if the patient has a known history of renal impairment[56]. Indeed, either International Normalized Ratio or serum creatinine are needed to consider rtPA in patients with Vitamin K-dependent or direct oral anticoagulants, respectively[56]. Idarucizumab, a humanized monoclonal antibody, has been available since 2015[57]; it binds to dabigatran, and it is capable of reversing its effects within a few minutes, with no hypercoagulable state afterward[58]. Its efficacy was proven in the RE-VERSE AD trial[59]. It is currently indicated for life-threatening bleeding, emergency surgery, and other urgent procedures[55], but, as of now, there are no indications in the most widely-known guidelines regarding its use in AIS, although this might change in a future revision of the major guidelines. Even if the patient does not meet the criteria for rtPA due to oral anticoagulation, they can still be candidates for MT[7]. The clinician must keep in mind that hemodialysis can be used to reverse the effect of any anticoagulant if the patient was otherwise a candidate for rtPA[56].

Table 4. Criteria for treatment with mechanical thrombectomy in < 6 h

1. Pre-stroke modified Rankin scale 0-1
2. Internal carotid artery oclussion, or at the M1 segment of the middle cerebral artery
3. Age > 18 years old
4. NIHSS ≥ 6
5. ASPECTS ≥ 6

Treatment can be initiated (groin puncture) within 6 h of symptom onset

NIHSS: National Institute of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score.

Thrombolysis and head trauma

Trauma, as a contraindication for rtPA, must be classified as either major non-intracranial trauma or as severe intracranial trauma. In AIS, patients with recent (14 days or less) major trauma that does not involve the head, may be carefully considered for rtPA, weighing the risk of bleeding from trauma-related injuries against the severity and potential disability due to a stroke (Class IIb, level of evidence C). Meanwhile, rtPA is contraindicated for patients with recent (within 3 months) severe head trauma and AIS (Class III, level of evidence C)[7].

Thrombolysis and recurrent stroke

The previous guidelines had a contraindication for rtPA within 4.5 h after symptom onset in patients with prior stroke in the previous 3 months, due to the alleged increased risk of intracranial hemorrhage[7]. However, recent studies have reported that rtPA for patients with small infarct volumes and functional independence might be considered even within 3 months of the previous stroke, with a low risk of symptomatic intracranial hemorrhage[60,61].

Stroke beyond 4.5 h

MT is indicated in those with proximal LVO of anterior circulation and, with a lower level of evidence, LVO in the posterior circulation. There is evidence of the benefits of MT in selected patients[62]. HERMES[3] is a meta-analysis of five clinical trials (MR CLEAN[63], ESCAPE[28], REVASCAT[30], SWIFT-PRIME[29], and EXTEND-IA[64]) that demonstrated the safety and efficacy of MT for LVO. In this analysis, 46% of selected patients treated with MT + rtPA achieved a mRS of < 2 at 90 days, when compared the 27% of those who only received rtPA (odds ratio [OR]: 2.49, confidence interval [CI] 95% 1.76-3.53; p < 0.0001). This is how the current

criteria for the "classic" window of 6 h for MT came to be. Table 4 summarizes the criteria for MT in these patients, in accordance with the 2019 update of the North American guidelines[7].

Reperfusion therapy from 6 to 24 h

Two clinical trials published in 2018 changed the paradigm of the treatment of AIS. Both of these studies are based on the concept of mismatch and had to be stopped early due to benefit from thrombectomy. DEFUSE 3[38] (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) demonstrated that if a patient with LVO has NIHSS > 6, and a small ischemic core (< 70 ml) with an extensive penumbra (penumbra: core ratio > 1.8), there is a great possibility of benefit with MT from 6 to 16 h from symptom onset. DAWN[37] (Thrombectomy 6-24 h after stroke with a mismatch between deficit and infarct) required LVO with NIHSS > 10, small core (stratified in different age groups, from < 21 ml to < 51 ml), which would cause a clinical-radiological mismatch. Both studies required the patient to be previously independent (mRS < 2 for DEFUSE 3, and mRS < 1 for DAWN) and used PWI. In DEFUSE 3, patients treated with MT at a median of 11 h, had a 28% increase in functional independence and an additional 20% absolute reduction in death or severe disability. These two trials used a proprietary automated software (RAPID) to determine the ischemic core and penumbra. The median time from symptoms to enrollment was 12.5 h in DAWN and 11 h in DEFUSE 3, and core volumes were < 10 mL; it is worth noting that the patients in both studies were very slow progressors. Effectiveness for late window thrombectomy was maintained across all subgroups of patients, including those defined by time, age, mode of presentation, and ASPECTS score. Undoubtedly, the results of DAWN and DEFUSE 3 have shown great benefit from MT in selected patients with AIS within a therapeutic window of 6-24 h. However, as suggested by the large treatment effect size observed in both trials, the clinical and imaging criteria were probably too strict[35,36]. In addition, not all hospitals that treat AIS have this specific software required in the inclusion criteria of both studies. However, physicians treating AIS patients should be familiar with this technique and its inclusion criteria, so as to offer the treatment to as many patients as possible, when appropriate.

Wake-up strokes and patients with an unknown time of symptom onset

Wake-up stroke includes patients that wake up with a focal deficit attributed to an AIS, while those that are simply found with an established deficit, with an unknown time from symptom onset, are deemed to have an AIS with unknown time of symptom onset. There are fundamental differences with therapeutic implications in these apparently all-too-similar stroke definitions. WAKE UP (MRI-Guided thrombolysis for stroke with unknown time of onset, 2018)[21] trial demonstrated the benefit of rtPA in both of these situations, with a median mRS of 1 after 90 days in the alteplase group, and 2 in the placebo group (adjusted common OR, 1.62; 95% CI, 1.17-2.23; p = 0.003); the trial used a DWI-FLAIR mismatch in the ischemic region to determine candidates for rtPA. The trial was stopped early due to funding issues, but the benefit was clear among those who received rtPA, as opposed to placebo.

EXTEND[65] (Thrombolysis Guided by Perfusion Imaging up to 9 h After Onset of Stroke) was published in May 2019, which assessed rtPA in a period defined by the researchers as the late window (4.5-9 h from symptom onset) in 225 patients. The primary outcome (mRS 0-1 at 90 days) occurred in 35.4% of the patients in the alteplase group and in 29.5% of the placebo group (adjusted risk ratio, 1.44; 95% CI, 1.01-2.06; p = 0.04). This trial evaluated cerebral perfusion using CTP. They concluded that these imaging modalities increased rtPA use, with the risk of more symptomatic hemorrhages (6.2% in the rtPA group and 0.9% in the placebo arm).

In patients with AIS on awakening or with a known time of onset and who have MRI DWI/FLAIR mismatch, the European guidelines suggest rtPA over no rtPA, even when the quality of evidence is moderate, and the strength of recommendation is weak[66].

Stroke units

Stroke units are equipped with continuous non-invasive monitorization, with trained personnel, and coordinated by neurologists who lead a multidisciplinary team. The AHA/ASA has demonstrated, with a level of evidence I, a reduction in mortality or dependency of 18%, compared to the hospitalization in general wards[23,67]. A British study reported that physicians working at stroke units are more likely to treat patients based on up-to-date evidence, with better functional outcomes[68]. There is also a Cochrane[69] review with similar results, with independent outcomes for age, gender, and stroke severity. To date, there are few

stroke units in our country, and, even in developed countries[70], the characteristics of stroke units are still not standardized, leading to varying results.

Future prospects

TNK is a new-generation fibrinolytic agent. This drug represents a promising alternative to rtPA as a thrombolytic treatment for patients with AIS. An important advantage of TNK over rtPA is the manner of administration, as TNK is applied in a single bolus, compared to rtPA that requires a bolus and a 60-min infusion[71]. EXTEND-IA TNK[72] (TNK vs. rtPA before Thrombectomy for Ischemic Stroke) randomized 202 patients with AIS who candidates for intravenous thrombolysis (either rtPA or TNK) were followed by MT. The primary endpoint was the demonstration of reperfusion greater than 50% of the ischemic territory, or absence of any retrievable thrombus. This outcome was reached in 22% of the TNK arm, and in 10% of the rtPA group, with no differences in symptomatic intracranial hemorrhage. The accepted dose for TNK to treat AIS depends on whether or not the patient will receive MT: 0.25 mg/kg if the patient will receive MT, and 0.40 mg/kg if the patient will not receive MT, with a maximum dose of 25 mg in a single intravenous bolus[7].

A number of trials mean to establish whether patients with less favorable imaging findings (i.e., with no DAWN or DEFUSE-3 criteria) could receive some degree of benefit from MT. Ongoing studies TESLA, SELECT 2, TENSION, and IN EXTREMIS, all use ASPECTS to define if MT is reasonable and safe for moderate to large infarcts, defined as ASPECTS 2-5[73]. Depending on the results, the number of candidates for reperfusion therapy could be greatly increased.

Conclusions

Intravenous thrombolysis continues to be the cornerstone of reperfusion therapy for AIS. LVOs are to be rapidly diagnosed and may have an even greater benefit with a combined therapy (rtPA + MT). Neurologists have a fundamental role in suspecting of LVO and confirming this suspicion using advanced neuroimaging; if proximal LVO is confirmed and the patient is within the therapeutic window from rtPA, the infusion must begin as soon as possible, while simultaneously alerting the team responsible for MT. The main function of the neurologist in the context of AIS is to not delay rtPA and to recognize LVO in a timely manner, so as to offer MT to all possible candidates, to achieve the maximum possible benefit. The implementation of algorithms to act according to the reality of each one of our hospitals is central for the proper diagnosis and treatment of patients with AIS caused or not by LVO.

Lessons to take home

1. Only 10-20% of AIS is due to LVO, but these are responsible for the greatest morbidity and mortality burden.
2. For patients with symptom onset between 3 and 4.5 h, one must mind the additional warning criteria for rtPA
3. In a patient with more than 4.5 h and LVO, must consider MT
4. In patients with symptom onset of < 4.5 h, no perfusion imaging is required
5. In a patient with 6-24 h of symptom onset, perfusion imaging should be performed to assess core and penumbra, so as to determine if the patient is a candidate to MT by DAWN or DEFUSE 3 criteria.
6. Wake-up stroke patients can receive rtPA only if they have a DWI-FLAIR mismatch, according to the WAKE-UP criteria
7. TNK is a promising alternative to rtPA and seems to have a better safety profile and to be easier to administrate. Its use in the clinical field is gradually increasing

Lessons to take home for physicians in Latin America

8. For patients with either wake-up stroke or stroke of undetermined time, should the receiving hospital only have NCCT, patients with ASPECTS 7-10 would benefit from a referral to a third-level hospital, where advanced neuroimaging may be implemented
9. Within the first 4.5 h from symptom onset, only NCCT with ASPECTS 7-10 is required to start rtPA
10. Given the possibility, the physician should obtain at least NCCT and CTA before referring a patient to a third-level hospital. CTP is required for AIS > 4.5 h, and it should be obtained if possible
11. If the physician detects a high NIHSS (≥ 6), they should consider referring the patient to a center with MT. rtPA must not be withheld if the patient meets criteria for thrombolysis

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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.

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References

1. Romano JG. Thrombolysis in Mexico-current status and opportunities. Rev Mex Neurocienc. 2019;20:208-9.
2. Lyden PD. Thrombolytic therapy for acute ischemic stroke. Stroke. 2019;50:2597-603.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723-31.
4. Malhotra K. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death : a review. Front Neurol. 2017;8:1-5.
5. Campbell BC, Berkhemer OA, Majoie CB, Dippel DW. Endovascular therapy for ischemic stroke. N Engl J Med. 2015;372:2363-6.
6. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 American heart association/American stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. Stroke. 2015;46:3020-35.
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke. Stroke. 2019;50:3331-2.
8. Yuh WT, Alexander MD, Ueda T, Maeda M, Taoka T, Yamada K, et al. Revisiting current golden rules in managing acute ischemic stroke: evaluation of new strategies to further improve treatment selection and outcome. Am J Roentgenol. 2017;208:32-41.
9. Kamalian S, Lev MH. Stroke imaging. Radiol Clin North Am. 2019;57:717-32.
10. Martins SC, Sacks C, Hacke W, Brainin M, de Assis Figueiredo F, Pontes-Neto OM, et al. Priorities to reduce the burden of stroke in Latin American countries. Lancet Neurol. 2019;18:674-83.
11. Arauz A, Mendez B, Soriano-Navarro E, Ruiz-Franco A, Quinzaños J, Rodríguez-Barragán M, et al. Thrombolytic therapy for acute stroke in Mexico-experience of four Mexican hospitals. Rev Mex Neurocienc. 2019;20:210-3.
12. León-Jiménez C, Ruiz-Sandoval JL, Chiquete E, Vega-Arroyo M, Arauz A, Murillo-Bonilla LM, et al. Tiempo de llegada hospitalaria y pronóstico funcional después de un infarto cerebral: resultados del estudio PREMIER. Neurologia. 2014;29:200-9.
13. Wu L, Wu W, Tali ET, Yuh WT. Oligemia, Penumbra, infarction: understanding hypoperfusion with neuroimaging. Neuroimaging Clin N Am. 2018;28:599-609.
14. Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. Neurophotonics. 2016;3:031411.
15. Sotoudeh H, Bag AK, Brooks MD. Code-stroke CT perfusion; challenges and pitfalls. Acad Radiol. 2019;26:1565-79.
16. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. Effects of alteplase beyond 3 h after stroke in the echoplanar imaging thrombolytic evaluation trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7:299-309.
17. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508-17.
18. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol. 2012;11:860-7.
19. Lui YW, Tang ER, Allmendinger AM, Spektor V. Evaluation of CT perfusion in the setting of cerebral ischemia: patterns and pitfalls. Am J Neuroradiol. 2010;31:1552-63.
20. Merino JG, Warach S. Imaging of acute stroke. Nat Rev Neurol. 2010;6:560-71.
21. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. MRI-guided thrombolysis for stroke with unknown time of onset. N Engl J Med. 2018;379:611-22.
22. Smith WS, Lev MH, English JD, Camargo EC, Chou M, Johnston SC, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and tia. Stroke; a J Cereb Circ. 2009;40:3834-40.
23. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. Stroke. 2018;49:e46-110.
24. Tseng MC, Chang KC. Stroke severity and early recovery after first-ever ischemic stroke: results of a hospital-based study in Taiwan. Health Policy. 2006;79:73-8.
25. Turc G, Maïer B, Naggara O, Seners P, Isabel C, Tisserand M, et al. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. Stroke. 2016;47:1466-72.
26. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet. 2000;355:1670-4.
27. Prakkamakul S, Yoo AJ. ASPECTS CT in acute ischemia: review of current data. Top Magn Reson Imaging. 2017;26:103-12.
28. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019-30.
29. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285-95.
30. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296-306.
31. Tei H, Uchiyama S, Usui T, Ohara K. Posterior circulation ASPECTS on diffusion-weighted MRI can be a powerful marker for predicting functional outcom. J Neurol. 2010;257:767-73.
32. Hextrum S, Biller J. Clinical distinction of cerebral ischemia and triaging of patients in the emergency department: mimics, wake-ups, late strokes, and chameleons. Neuroimaging Clin N Am. 2018;28:537-49.
33. Brinjikji W, Demchuk AM, Murad MH, Rabinstein AA, McDonald RJ, McDonald JS, et al. Neurons over nephrons. Stroke. 2017;48:1862-8.
34. Tsivgoulis G, Katsanos AH, Schellinger PD, Köhrmann M, Varelas P, Magoufis G, et al. Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions. Stroke. 2018;49:232-5.
35. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke. 2011;42:1775-7.
36. Bang OY, Saver JL, Kim SJ, Kim GM, Chung CS, Ovbiagele B, et al. Collateral flow averts hemorrhagic transformation after endovascular therapy for acute ischemic stroke. Stroke. 2011;42:2235-9.
37. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2017;378:11-21.
38. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378:708-18.
39. Vagal A, Foster LD, Menon BK, Livorine A, Shi J, Qazi E, et al. Multimodal CT imaging: time to treatment and outcomes in the IMS III trial. Am J Neuroradiol. 2016;37:1393-8.
40. Vagal A, Meganathan K, Kleindorfer DO, Adeoye O, Hornung R, Khatri P. Increasing use of computed tomographic perfusion and computed tomographic angiograms in acute ischemic stroke from 2006 to 2010. Stroke. 2014;45:1029-34.
41. Shen J, Li X, Li Y, Wu B. Comparative accuracy of CT perfusion in diagnosing acute ischemic stroke: a systematic review of 27 trials. PLoS One. 2017;12:1-17.
42. Souza LC, Chaudhry SA, Payabvash S, Yoo AJ, Kemmling A, Schaefer PW, et al. Malignant CTA collateral profile is highly specific for large admission DWI infarct core and poor outcome in acute stroke. AJNR Am J Neuroradiol. 2012;33:1331-6.
43. Leslie-Mazwi TM, Hirsch JA, Falcone GJ, Schaefer PW, Lev MH, Rabinov JD, et al. Endovascular stroke treatment outcomes after patient selection based on magnetic resonance imaging and clinical criteria. JAMA Neurol. 2016;73:43-9.
44. Bang OY, Goyal M, Liebeskind DS. Collateral circulation in ischemic stroke: assessment tools and therapeutic strategies. Stroke. 2015;46:3302-9.
45. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34:2774.
46. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, Von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement and for the cerebral angiographic revascularization, grading (CARG) collaborators, STIR revascularization working group, and STIR thrombol. Stroke. 2013;44:2630-63.
47. Sheth SA, Liebeskind DS. Collaterals in endovascular therapy for stroke. Curr Opin Neurol. 2015;28:10-5.
48. Rost NS, Bottle A, Lee JM, Randall M, Middleton S, Shaw L, et al. Stroke severity is a crucial predictor of outcome: an international prospective validation study. J Am Heart Assoc. 2016;5:1-7.

49. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol. 1992;32:78-86.
50. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabín J. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke. 2004;35:486-90.
51. Mazighi M, Chaudhry SA, Ribo M, Khatri P, Skoloudik D, Mokin M, et al. Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. Circulation. 2013;127:1980-5.
52. Demchuk AM, Goyal M, Yeatts SD, Carrozzella J, Foster LD, Qazi E, et al. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the interventional management of stroke III trial. Radiology. 2014;273:202-10.
53. Flottmann F, Leischner H, Broocks G, Nawabi J, Bernhardt M, Faizy TD, et al. Recanalization rate per retrieval attempt in mechanical thrombectomy for acute ischemic stroke. Stroke. 2018;49:2523-5.
54. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN, Starr M, Mejilla J, et al. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits the PRISMS randomized clinical trial. J Am Med Assoc. 2018;320:156-66.
55. Fang CW, Te TY, Chou PC, Chen HM, Lu CM, Tsao CR, et al. Intravenous Thrombolysis in acute ischemic stroke after idarucizumab reversal of dabigatran effect: analysis of the cases from Taiwan. J Stroke Cerebrovasc Dis. 2019;28:815-20.
56. Seiffge DJ, Polymeris AA, Fladt J, Lyrer PA, Engelter ST, De Marchis GM. Management of patients with stroke treated with direct oral anticoagulants. J Neurol. 2018;265:3022-33.
57. Baule A, Cabigiosu F, Zanda B, Sanna A, Mongili C, Manca A. Thrombolysis in Acute ischemic stroke after idarucizumab for dabigatran etexilate reversal in elderly: a case report. J Vasc Interv Neurol. 2018;10:15-7.
58. Meyer D, Chu F, Derry K, Hailey L. Acute reversal of dabigatran with idarucizumab for intravenous thrombolysis as acute stroke treatment. J Clin Neurosci. 2019;59:355-7.
59. Pollack CV, Reilly PA, Van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal-full cohort analysis. N Engl J Med. 2017;377:431-41.
60. Kahles T, Mono ML, Heldner MR, Baumgartner RW, Sarikaya H, Luft A, et al. Repeated intravenous thrombolysis for early recurrent stroke: challenging the exclusion criterion. Stroke. 2016;47:2133-5.
61. Wu C, Wu D, Chen J, Li C, Ji X. Why not intravenous thrombolysis in patients with recurrent stroke within 3 months? Aging Dis. 2018;9:309-16.
62. Fransen PS, Beumer D, Berkhemer OA, Van Den Berg LA, Lingsma H. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands : study protocol for a randomized controlled trial. Trials. 2014;15:343.
63. Berkhemer OA, Fransen PS, Beumer D, Van Den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20.
64. Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, et al. Endovascular Therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009-18.
65. Ma H, Campbell BC, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med. 2019;380:1795-803.
66. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European stroke organisation (ESO)-European society for minimally invasive neurological therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by stroke alliance for Europe (SAFE). Eur Stroke J. 2019;4:6-12.
67. de Leciñana MA, Egido JA, Casado I, Ribó M, Dávalos A, Masjuan J, et al. Guía para el tratamiento del infarto cerebral agudo. Neurologia. 2014;29:102-22.
68. Ramsay AI, Morris S, Hoffman A, Hunter RM, Boaden R, McKevitt C, et al. Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England. Stroke. 2015;46:2244-51.
69. Langhorne P, Ramachandra S, Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke (Review). Cochrane Rev. 2013;11:2-3.
70. Rac VE, Sahakyan Y, Fan I, Ieraci L, Hall R, Kelloway L, et al. The characteristics of stroke units in Ontario: a pan-provincial survey. BMC Health Serv Res. 2017;17:1-10.
71. Rønning OM, Logallo N, Thommessen B, Tobro H, Novotny V, Kvistad CE, et al. Tenecteplase versus alteplase between 3 and 4.5 hours in low national institutes of health stroke scale. Stroke. 2019;50:498-500.
72. Campbell BC, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378:1573-82.
73. Phipps MS, Cronin CA. Management of acute ischemic stroke. BMJ. 2020;368:1-15.