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Neuroprotective strategies in COVID-19

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ABSTRACT

Considering the Release published by the Cuban Academy of Sciences in the face of the enormous local and global challenges associated with the COVID-19 pandemic, it is necessary that all the Cuban scientific community be placed in the management and investigation of this disease. Since the XVI century our country has been confronting epidemic outbreaks in political and social conditions very different from what we now have. SARS-CoV-2 (CoV-2) is the new coronavirus, which causes the disease coined by WHO as COVID-19 since February 2020. Different countries have reported CNS manifestations, but neuroprotective strategies have not been implemented. In the present article we provide a brief overview of the neurological manifestations which have been reported during the COVID-19 pandemic. We also highlight the importance not only of treating the immediate damage to the CNS caused by the virus in these patients, but also suggest the introduction of a neuroprotective agent, such as intranasal Neuro-EPO –a Cuban molecule capable of potentiating the endogenous defenses of the brain– which could prove to be effective in locally diminishing the immediate and possibly long term damage of the virus on the nervous system.

Estrategias neuroprotectoras en la COVID-19

Palabras clave

COVID-19, SARS-CoV-2, pandemia, neuroprotección, síntomas neurológicos.

RESUMEN

Considerando la publicación publicada por la Academia Cubana de Ciencias ante los enormes desafíos locales y globales asociados con la pandemia de COVID-19, es necesario que toda la comunidad científica cubana se coloque en el manejo e investigación de esta enfermedad. Desde el siglo XVI, nuestro país ha enfrentado brotes epidémicos en condiciones

políticas y sociales muy diferentes de las que tenemos ahora. El SARS-CoV-2 (CoV-2) es el nuevo coronavirus, que causa la enfermedad acuñada por la OMS como COVID-19 desde febrero de 2020. Diferentes países han informado manifestaciones del SNC, pero no se han implementado estrategias neuroprotectoras. En el presente artículo proporcionamos una breve descripción de las manifestaciones neurológicas que se han informado durante la pandemia de COVID-19. También destacamos la importancia no solo de tratar el daño inmediato al SNC causado por el virus en estos pacientes, sino que también sugerimos la introducción de un agente neuroprotector, como el Neuro-EPO intranasal, una molécula cubana capaz de potenciar las defensas endógenas de El cerebro, que podría ser eficaz para disminuir localmente el daño inmediato y posiblemente a largo plazo del virus en el sistema nervioso.

INTRODUCTION

Since the XVI century our country has suffered different epidemic outbreaks historically based in the conquest and colonization. This modified the Cuban epidemiological situation through the introduction of new diseases, such as smallpox, measles and yellow fever, that caused numerous outbreaks during the XVI, XVII and XVIII centuries, with high mortality rates that led to a rapid extermination of the native population. Among other factors, bad hygiene, climate, increase of seaport activities concomitant with population growth, also contributed to epidemics in those centuries. [1-9]

More recently, and in very different socio-political conditions after the triumph of the revolution and its policy of health for all, an explosive outbreak of hemorrhagic dengue occurred in May 1981. It lasted slightly more than 4 months, and 344 203 cases were reported. The week with the highest incidence was from June 29 to July 6, when 9447 cases were reported. Virological studies determined that the epidemic was caused by serotype 2 dengue virus.[10]

Today our country is being hit by a pandemic caused by a new viral agent that has evidenced the many inequalities and flaws in our planet, including the richest countries. SARS-CoV-2 (CoV-2) is the new coronavirus causing the disease coined by the World Health Organization as coronavirus disease-19 (COVID-19) in February 2020. The expansion of this novel virus which first appeared in Wuhan, China, has led to the COVID-19 pandemic, which constitutes the most severe threat to global public health systems since the Spanish flu outbreak in 1918, and has rapidly captured worldwide attention.[11] To date more than 5 million people in the world have been infected, and nearly 325 000 have died as a consequence of COVID-19. Hence, a great deal has to be done in order to minimize its impact, and what´s even more important, to control it.

The main manifestations of COVID-19 are flu-like symptoms (fever, cough, myalgia, fatigue), some patients eventually develop dyspnea, followed in approximately 15-19 % of the patients by moderate to severe respiratory distress, which can lead to death. While respiratory symptoms are the most frequent, they are not the only ones at onset or during the course of the disease. Other organic systems (i.e., digestive and nervous systems) have heralded SARS-CoV-2 infection in some cases.[11-13]

DISCUSSION

Neurological manifestations of COVID-19

In a series of 214 COVID-19 patients with acute respiratory syndrome due to SARS-CoV-2 infection from Wuhan, China, nervous system manifestations were reported in 36,4 % of patients, being more frequent in cases with severe forms. Central nervous system (CNS) symptoms were the most frequently reported (24,8 %), but peripheral nervous system and skeletal muscle injury were also present.[12] Other authors have also described neurological manifestations in patients with severe COVID-19, amongst which agitation, confusion and diffuse corticospinal tract signs prevailed, with one third of them presenting dysexecutive syndrome at discharge.[14]

The first report of Guillain–Barré Syndrome (GBS) possibly associated with COVID-19 occurred in a patient returning from Wuhan, with the peculiarity of it appearing 7 days before the presentation of respiratory symptoms, and testing positive for SARS-CoV-2. The authors suggested a par infectious pattern, as reported previously in other coronavirus infections. [15] Soon after, five cases with GBS after the onset of COVID-19 were reported in Italy.[16] Furthermore, the first presumptive case of encephalitis linked to COVID-19 was documented in the USA, where brain MRI images revealed a rare complication

of influenza known as acute necrotizing encephalopathy, in a patient diagnosed with COVID-19 infection.[17] This condition has not been associated with direct viral invasion, but to cytokine storms and the over-production of immune cells leading to breakdown of the blood-brain barrier.[17,18]

In a series of 214 COVID-19 patients hospitalized in Wuhan, China, acute cerebrovascular disease was reported in 5,7 % of severe SArs-COV-2 patients;[12] while coagulopathy was among the risk factors for mortality encountered in a cohort of 191 COVID-19 patients also from Wuhan.[19] Later, the Mount Sinai Health System in New York reported total of five patients younger than 50 years of age presenting with large vessel acute strokes and testing positive for COVID-19 during a two-week period, a frequency much higher than that observed in the previous year´s registry[20]. A clear association between acute inflammatory events and stroke has been reported,[21] as well as an increase in the risk of stroke 2-4 weeks after acute infection with flu-like illnesses.[22] A noteworthy and detailed analysis of the possible association between COVID-19 and stroke was recently published.[23]

Perhaps one of the most common neurological symptoms associated with COVID-19 are olfactory and taste disorders.[24] In the Wuhan series it was reported in approximately 5 % of hospitalized patients.[12] Aside from being fairly frequent in patients with COVID-19 –as in other viral infections– these symptoms may precede the onset of clinical disease, and might be useful as a clinical screening tool for testing apparently asymptomatic individuals.[25]

The neuroinvasive potential of SARS-CoV-2 has been considered to be involved in the pathophysiology of acute respiratory failure appearing in some COVID-19 patients, possibly through intranasal entrance of the virus to the brain via the olfactory nerves, spreading thereafter to specific brain areas such as thalamus and brainstem.[26,27]

As most coronaviruses have similar viral structure and infection pathways, it is believed that they probably share analogous infection mechanisms, which may also be valid for SARS-CoV-2. [26]

Genomic analysis shows that SARS-CoV-2 shares highly homological sequence with SARS-CoV. [28] It uses the same receptor as SARS-CoV for entry into the cell –the receptor for angiotensin converting enzyme-2 (ACE2)– present on the surface of epithelial cells in the lung, intestine, kidney, and blood vessels. Furthermore, priming of the spike (S) protein of coronaviruses by the serine protease TMPRSS2, which facilitates viral attachment to the surface of target cells, enhances its binding to the ACE2 receptor.[29]

Viruses reach the brain through various pathways: 1) retrograde axonal transport along axons, 2) hematogenous spread via the brain barriers (blood-brain barrier (BBB), blood-cerebrospinal fluid barrier, meningeal-cerebrospinal fluid barrier), 3) direct infection of endothelial cells or 4) spreading of infected leukocytes to the brain across the BBB. [30] The exact mechanisms by which SARS-CoVs reach the CNS remain unclear, probably involving transneuronal and hematogenous routes.[31]

Viral particles have been long known to hijack retrograde axonal transport along the microtubules and to spread between neurons, thus gaining access to the nervous system. [32] SARS-CoV particles were observed in brain samples from SARS patients, being located almost exclusively in the neurons.[33] On the other hand, experimental studies in transgenic mice revealed that when SARS-CoV was administered intranasally, it entered the brain, possibly via the olfactory nerves.[34]

Brain damage by SARS-CoV-2 could be due to the attack of endothelial cells in the cerebral blood vessels, where ACE2 is highly expressed, causing breakdown and thus increased permeability of the blood-brain barrier (BBB), cerebral edema, and intracranial hypertension. Although the blood-brain barrier (BBB) protects the CNS from the events occurring in the periphery, it can be breached by the virus and/or the inflammatory processes which subsequently ensue, or it can be circumvented at more vulnerable sites, as in terminal nerve endings (i.e. the olfactory nerves). Furthermore, a disrupted BBB may promote invasion of infected peripheral cells into brain tissues and neurons. Another mechanism possibly participating in brain tissue destruction is the secretion of cytokines from infected neurons, when the virus invades the nervous system. [31,34]

Nevertheless, acute nervous system involvement in COVID-19 is not the only issue troubling researchers. Possible long-term neurological effects have also been a concern, considering the large amount of individuals who have been affected worldwide. Among these, emotional and cognitive changes have been considered.[14,35] Furthermore, the axonal transport of neurotropic viruses could cause basically disordered proteins, such as α-synuclein to bind and form toxic aggregates that are conveyed along neuronal pathways, causing cell death at specific brain regions. [35]

It is known that the inflammatory response which accompanies acute or chronic infection may trigger mechanisms underlying the early stages of neurodegenerative disorders via impaired BBB function. Thus, systemic inflammation secondary to SARS-CoV-2 infection could also contribute to neuroinflammatory processes that could lead to the occurrence of long term neurological syndromes in susceptible individuals. Longitudinal studies to evaluate the incidence of neurodegenerative disorders following the COVID-19 pandemic have been recommended. [36]

Therapeutic approach to SARS-CoV-2 infection and the nervous system

Antiviral and symptomatic supportive treatments are normally administered in hospitalized COVID-19 patients, and additional therapeutic actions are taken when nervous system symptoms occur, depending on the type of CNS involvement. A very important aspect to keep in mind is that SARS-CoV-2 infection of specific brain structures could be responsible to some extent for acute respiratory failure. [26] On the other hand, neurological symptoms are potential indicators of poor prognosis, and prevention and treatment of CNS infection have been suggested to be important to reduce respiratory symptoms and acute respiratory failure, as well as to improve the prognosis of COVID-19. [37]

Considering that additionally SARS-CoV-2 infection could have as yet not known long term effects on the CNS that could predispose the hosts to neurodegenerative disorders, implementing neuroprotective strategies could prove to be important not only as a supportive treatment of CNS complications –essential for patients´ recovery–, but also to prevent long term effects on the CNS.

Bearing in mind the potential neuroinvasion of SARS-CoV-2 via the olfactory nerves, and the evidence directly linking COVID-19 with early manifestations of smell and taste impairment, the use of an intranasally applied neuroprotective agent, capable of potentiating the endogenous defenses of the brain in the infected patient[38] could prove to be effective in locally diminishing the damaging action of the virus on the olfactory nerves. Furthermore, it could also have a neuroprotective action on the nervous structures linked to this pathway in the brain.

One of the challenges Cuba has in this line of work is nasal Neuro-EPO (recombinant human erythropoietin with low sialic acid content), which has been widely evaluated in pre-clinical studies in a series of disorders of the CNS[39-55] and in a Phase 1 clinical trial which proved its use in healthy volunteers was safe. [56] At present a clinical trial in Alzheimer´s disease is in course, [57] while other preclinical studies for other CNS diseases are ongoing. [55,58-63]

Potentiation of endogenous neuroprotection is the challenge the authors propose to counteract the molecular unbalance that occurs when endogenous and exogenous agents alter homeostasis in the CNS. A simplified representation of this action is presented in figure 1.

Taking into account the clinical evidence and the findings implicating the nervous system as a target in COVID-19,

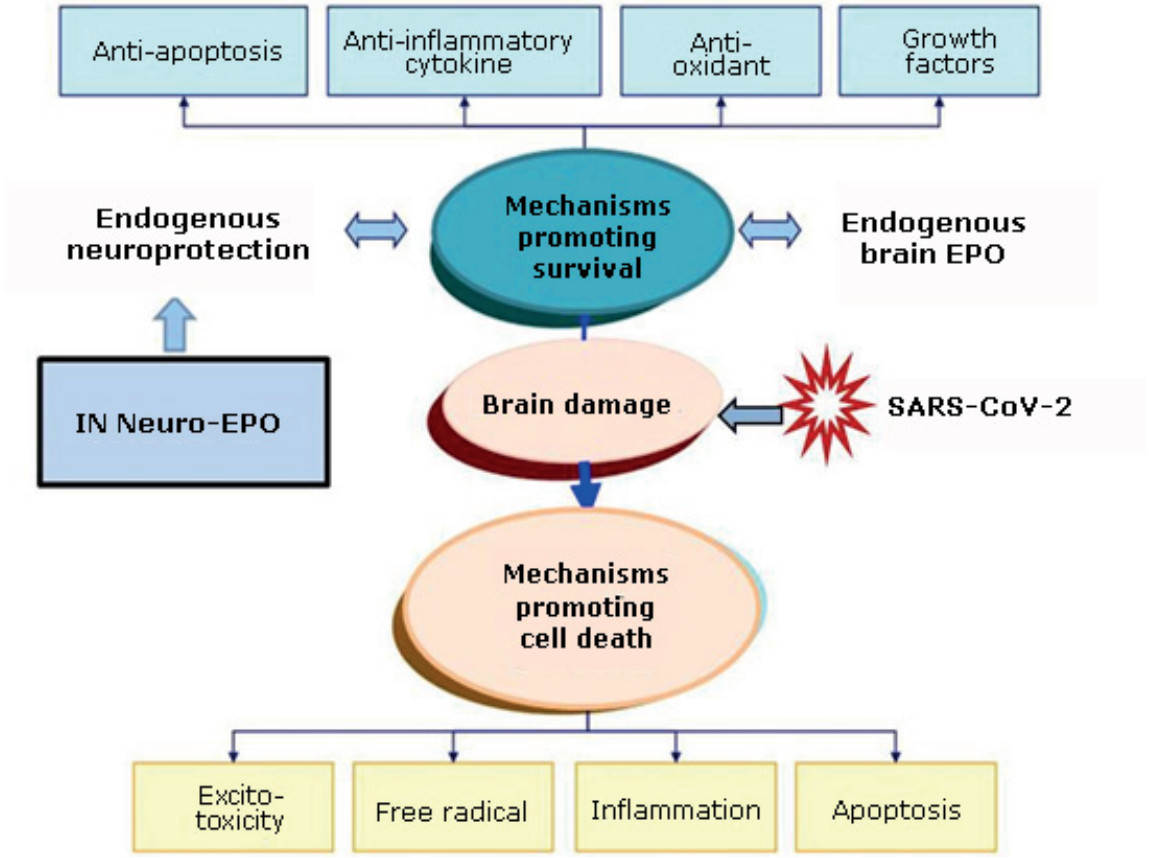

Fig. 1. Simplified schematic representation of the mechanisms through which intranasal (IN) Neuro-EPO modulates endogenous neuroprotection in SARS-CoV-2 infection. When its levels are affected in a cerebral region, by endogenous or exogenous xenobiotics, mechanisms that promote neuronal death are unleashed. When brain EPO levels are preserved, endogenous neuroprotective mechanisms prevail.

protecting the CNS should be a therapeutic alternative in pre-symptomatic or initial stages of the disease. This might contribute to reduce neurologic complications during the course of the disease, especially in those patients who are at higher risk because of natural reasons (age) or because of the associated co morbidities.

CONCLUSIONS

SARS-CoV-2 infection is associated with different pathological manifestations of the nervous system as an expression of direct nervous tissue damage by the virus together with the neuroinflammatory reaction accompanying viral invasion, or as an expression of post-infectious damage. Treatment of CNS infection has been suggested to be crucial in reducing respiratory symptoms and acute respiratory failure, as well as to improve the prognosis of COVID-19. Furthermore, the association of a neuroprotective agent, such as intranasal Neuro-EPO, capable of potentiating the endogenous defenses of the brain in the infected patient, could prove to be effective in locally diminishing the immediate and long term damage of the virus on the nervous system.

BIBLIOGRAPHIC REFERENCES

1. Callejas Obispo S, Loyola Vega O, Díaz Pendás H, López Civeira F, Rodríguez Ben JA. Historia de Cuba. 2da ed. La Habana: Editorial Pueblo y Educación, 2010.
2. Bombino Ruíz E, Pérez Pino L. Historia de las epidemias durante la etapa colonial: Fiebre amarilla, Viruela y otras enfermedades. Cuba: Monografías.com; 2014 [accessed: 12 Oct 2016]. http://www.monografias.com/trabajos103/historia-epidemias-etapa-colonial-fiebreamarilla-viruela-y-otras-enfermedades/historia-epidemias-etapa-colonial-fiebreamarilla-viruela-y-otras-enfermedades.shtml
3. Beldarrain Chaple E. Apuntes sobre la medicina en Cuba. Historia y aplicaciones. 1ra ed. La Habana: Ecimed; 2005.
4. Beldarrain Chaple E. Las epidemias y su enfrentamiento en Cuba. La Habana [tesis]. Centro Nacional de Información de Ciencias Médicas; 2010.
5. Delgado García G. Siglo XVI Bojeo, conquista y colonización de Cuba: Las primeras villas. Primeras epidemias. Ataques de corsarios y piratas. Primeras noticias médicas de las Actas del Cabildo de La Habana. Cuad Hist Salud Pública. 2004 [accessed: 01 Nov 2016]; (96). http://scieloprueba.sld.cu/scielo.php?script=sci_arttext&pid=S0045- 91782004000200006&lng=es
6. Capdepont Ballina JL, Díaz Perera MA. La viruela en Tabasco: impacto y medidas preventivas (1890-1915). Tzintzun. Rev. Estud. Históricos 2014 [accessed: 01 Nov 2016]; (59). http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1870-719X2014000100003&lang=pt
7. Delgado García G. La salud pública en Cuba durante el periodo colonial español. Cuad Hist Sal Pub. 1996; (8).
8. Hernández Espinosa PO. El sarampión y la mortalidad infantil en el Distrito de Hermosillo en 1898. Un ensayo de antropología demográfica. Cuicuilco. 2015 [accessed: 01 Nov 2016]; 22(63): 273-92. http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0185- 16592015000200011&lang=pt
9. Muscat M, Ben Mamou M, Shefer A, Jankovic D, Deshevoy S, Butler R. Situación del sarampión y la rubéola en la Región Europea de la OMS. Rev Esp Salud Pública 2015. [accessed: 01 Nov 2016]; 89(4): 345-51. http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1135- 57272015000400002&lng=en
10. Kozti G, Guzmád MG, Brmo J.Dengue hemorrágicoen Cuba. Crónica de una epidemia. Bol of Saint Panam.1986;100 (3).
11. 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. 2020; Feb 24; doi: 10.1001/jama.2020.2648.
12. 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; doi:10.1001/jamaneurol.2020.1127
13. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. NEJM. 2020; April 17. DOI: 10.1056/NEJMc2010419
14. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. NEJM.2020; April 15. DOI: 10.1056/NEJMc2008597
15. 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; April 1. https://doi.org/10.1016/S1474-4422(20)30109-5
16. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré Syndrome associated with SARS-CoV-2. NEJM. 2020; April 17. DOI: 10.1056/NEJMc2009191
17. 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; Mar 31:201187. doi: 10.1148/radiol.2020201187.
18. Moore J B, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020; 10.1126/science.abb8925
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1054-62.
20. 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; May 14;382(20):e60. doi: 10.1056/NEJMc2009787.
21. Warren-Gash C BR, Whitaker H, McMenamin J, Hayward AC. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. Eur Respir J. 2018;51.doi: 10.1183/13993003.01794-2017
22. Elkind MSV, Carty CC, O'Meara ES, Lumley T, Lefkowitz D, Richard A. Kronmal, et al. Hospitalization for infection and risk of acute ischemic stroke: the Cardiovascular Health Study. Stroke. 2011;42:1851–6.DOI: 10.1161/STROKEAHA.110.60858
23. Valdes Valderrama E, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. Stroke. 2020;51:00-00. doi: 10.1161/STROKEAHA.120.030153.

24. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology. 2020 Apr 2. doi: 10.4193/Rhin20.114.
25. 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;March. doi:10.1093/cid/ciaa330
26. Li Y-C, Bai W-Z, 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; Feb 27. doi: 10.1002/jmv.25728.
27. Machado Curbelo C. Severe COVID-19 Cases: Is Respiratory Distress Partially Explained by Central Nervous System Involvement? MEDICC Review. 2020; 22(2): 38-9.
28. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes Infect. 2020; pii: S1286-4579(20)30025-3.
29. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 2020; 181, 271–80. https://doi.org/10.1016/j.cell.2020.02.052
30. Ludlow M, Kortekaas J, Herden C, Hoffmann B, Tappe D, Trebst C, et al. Neurotropic virus infections as the cause of immediate and delayed neuropathology. Acta Neuropathol.2016; 131:159–84. doi: 10.1007/s00401-015-1511-3
31. 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; https://dx.doi.org/10.1021/acschemneuro.0c00122
32. Taylor MP, Enquist LW. Axonal spread of neuroinvasive viral infections. Trends Microbiol. 2015; 23(5):283-8. doi: 10.1016/j.tim.2015.01.002.
33. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin Infect Dis. 2005; 41:1089-96.https://doi.org/10.1086/444461
34. 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.
35. 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. doi: 10.3389/fneur.2020.00308.
36. De Felice FG, Tovar-Moll F, Moll J, Munoz DP, Ferreira ST. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System. Trends Neurosci. 2020; Apr 21. pii: S0166-2236(20)30091-6. doi: 10.1016/j.tins.2020.04.004.
37. Li H,Xue Q, Xu X. Involvement of the Nervous System in SARS-CoV-2 Infection. Neurotox Res. 2020; https://doi.org/10.1007/s12640-020-00219-8
38. García Rodríguez JC (Editor): Neuroprotección en enfermedades Neuro y Heredo degenerativas. Barcelona, España: Omnia Science; 2014. pp.1-292. ISBN: 978-84-941872-3-0.
39. Sosa Testé I, García Salman JD, Subiros N, González C, Rodríguez Y, García Rodríguez JC. Alternativa terapéutica en la isquemia cerebral empleando la Eritropoyetina humana recombinante (rHu-EPO CIM) como neuroprotector. Rev. CNIC.2005; Vol. 36 (Numero Especial).
40. Subiros N, García Rodríguez JC, González B, Sosa I, García Salman JD. Evaluación histológica del efecto de la Eritropoyetina vía intranasal, sobre la muerte neuronal retardada en gerbos sometidos a isquemia cerebral transitoria. Estudio preliminar (2005) http://www.conganat.org/7congreso/final/vista_trabajo=445 pdf
41. García Rodríguez JC, Miranda Quintana JA. Carta al Editor de Revista CNIC. Rev CNIC Ciencias Biológicas.2005; 36 (2).
42. González C, Sánchez A. González-Quevedo A, Delgado R, Velázquez L, García Rodríguez JC. Serum and cerebrospinal fluid levels of Cu, Fe and Zn in patients with type SCA-2 Ataxia from Province of Holguín Cuba. Therapeutic Basic. Dialogue Clin Neurosc. 2005; 3 (4). ISSN 1294-8322.
43. González C, Sánchez A. González-Quevedo A, R. Delgado R, Velázquez L, García Rodríguez JC.Serum and cerebrospinal fluid levels of Cu, Fe and Zn in patients with type SCA-2 Ataxia from Province of Holguín Cuba. One Year Later. Rev CNIC. 2006; 37 (Numero Especial).
44. Sosa Testé I, García Rodríguez JC, García JD. New goal in ischemia stroke therapy:rHu-EPO nasal application. (2006) Rev. Acta Pharmacol. Sin,2006; 27 (Suppl 1): 97.
45. Sosa Testé I, García Salman JD, Cruz J, Santana J, Subirós N, González Triana C, et al. La vía nasal para la administración de fármacos al cerebro. Evidencias del efecto neuroprotector de la eritropoyetina en animales de laboratorio. (2006) Pub. Corta en el CD del evento Panvet.
46. Sosa Testé I, García Rodríguez JC, García Salman JD, Santana J, Subiros Martínez N, González Triana C, et al. Intranasal administration of recombinant human erythropoietin exerts neuroprotective effects on post-ischemic brain injury in mongolian gerbils. Pharmacologyonline. 2006; 1:100-12
47. García Rodríguez JC, Sosa Testé I. The nasal Route as a Potential Pathway for Delivery of Erythropoietin in the treatment of Acute Ischemic Stroke in Humans. The Scientific World J. 2009;9: 970-81.
48. Rodríguez Cruz Y, Mengana Támos Y, Muñoz Cernuda A, Subirós Martínez N, González-Quevedo A, Sosa Testé I, et al. Treatment with Nasal Neuro-EPO Improves the Neurological, Cognitive, and Histological State in a Gerbil Model of Focal Ischemia. The Scientific World J. 2010;10: 2288–300.
49. García Rodríguez JC, Rodríguez-Cruz Y. The Therapeutic Potential of Neuro-EPO Administered Nasally on Acute Cerebrovascular Disease. Current Psychopharmacology. 2012; 1 (3): 228-32.
50. Lagarto Parra A,García Rodríguez JC. Nasal Neuro EPO could ba a Reliable Choice for Neuroprotective Stroke Treatment. Central Nervous System Agent in Medicinal Chemistry. 2012; 12: 60-8.
51. Garzón F, Rodríguez Y, GarcíaJC, Rama R. Neuroprotective Effects of neuro-EPO Using an in Vitro Model of Stroke. Behav Sci. 2018; 8, 26: doi:10.3390/bs8020026.
52. Merelli A, García Rodríguez JC; Folch J; RegueiroMR, Camins A, Lazarowski, A. Understanding the Role of Hypoxia Inducible Factor During Neurodegeneration for New Therapeutics Oppor-

tunities. Cur Neuropharmacol.2020; 16 (10): 1484-98. https://doi.org/10.2174/1570159X16666180110130253
53. Garzón F, Coimbra D, Parcerisas A, Rodríguez Y, García Rodríguez JC, Soriano E,et al. NeuroEPO Preserves Neurons from Glutamate-Induced Excitotoxicity. J Alzheimer's Dis. 2018; 65: 1469–83 doi: 10.3233/JAD-180668.
54. Rama R, Garzón F, Rodríguez Y, Maurice T, García Rodríguez JC. Neuroprotective effect of Neuro-erythropoietin in neurodegenerative diseases: "Alea jacta est". Neural Regen Res. 2019; 14(9):1519-21 Doi:10.4103/1673-5374.255968.
55. Auzmendi J, Puchulu MB, García Rodríguez JC, Balaszczuk AM, Lazarowski A and Merelli A. "EPO and EPO-Receptor System as Potential Actionable Mechanism for the Protection of Brain and Heart in Refractory Epilepsy and SUDEP" Cur Pharmaceut Design. 2020; 26: 1-9. doi:10.2174/1381612826666200219095548
56. Santos-Morales O, Díaz-Machado A, Jiménez-Rodríguez D, Pomares-Iturralde Y, Festary-Casanovas T, González-Delgado CA, et al.Nasal administration of the neuroprotective candidate NeuroEPO to healthy volunteers: a randomized, parallel, open-label safety study. BMC Neurol. 2017;17(1):129. doi: 10.1186/s12883-017-0908-0.
57. Eficacia y seguridad de la administración nasal de NeuroEPO en el tratamiento de los pacientes con enfermedad de Alzheimer leve/moderado. Ec fase II-III. RPCEC00000233 (República de Cuba Ensayo Clínico 00000233) 2019.
58. Maurice T, Mustafa M-H, Desrumaux C, Keller E, Naert G, García-Barceló MC, et al. Intranasal formulation of erythropoietin (EPO) showed potent protective activity against amyloid toxicity in the A β25-35 non-transgenic mouse model of Alzheimer's disease. J Psychopharmacol.2013;27(11): 1044 –57.
59. Rodríguez Cruz Y, Strehaiano M, Rodríguez Obaya T, García Rodríguez JC, Maurice T. An Intranasal Formulation of Erythropoietin (Neuro-EPO) Prevents Memory Deficits and Amyloid Toxicity in the APPSwe Transgenic Mouse Model of Alzheimer's Disease. J Alzheimer's Dis.2017;55: 231–48 doi: 10.3233/JAD-160500 IOS
60. Garzón F, Rodríguez Y, Garcia Rodríguez JC, Rama R. Neuroprotective Effects of neuro-EPO Using an In Vitro Model of Stroke. Behav Sci. 2018; 8, 26; doi:10.3390/bs8020026.
61. Merelli A, García Rodríguez JC, Folch J, Regueiro MR, Camins A, Lazarowski A. Understanding the Role of Hypoxia Inducible Factor During Neurodegeneration for New Therapeutics Opportunities. Cur Neuropharmacol.2020;16 (10): 1484-98. https://doi.org/10.2174/1570159X16666180110130253
62. Garzón F, Coimbra D, Parcerisas A, Rodríguez Y, García JC, Soriano E, et al. NeuroEPO Preserves Neurons from Glutamate-Induced Excitotoxicity. J Alzheimer's Dis.2018;65: 1469–83. doi 10.3233/JAD-180668.
63. Rama R, Garzón F, Rodríguez Y, Maurice T, García Rodríguez JC. Neuroprotective effect of Neuro-erythropoietin in neurodegenerative diseases: "Alea jacta est". Neural Regen Res. 2019; 14(9):1519-21 doi:10.4103/1673-5374.255968.