

FAVORABLE OUTCOME OF SARS-COV-2 INFECTION IN A PATIENT WITH PITUITARY INSUFFICIENCY

EVOLUCIÓN FAVORABLE DE LA INFECCIÓN POR SARS-COV-2 EN UNA PACIENTE CON INSUFICIENCIA HIPOFISARIA

CURSO FAVORÁVEL DE INFECÇÃO POR SARS-COV-2 EM PACIENTE COM INSUFICIÊNCIA HIPOFISÁRIA

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El nuevo coronavirus causante de la enfermedad pandémica conocida como COVID-19, está generando un desafío sin precedentes en los sistemas de salud de todo el mundo. Dicho escenario puede favorecer el deterioro en el control de las patologías crónicas por la dificultad en el acceso al sistema sanitario. El hipopituitarismo o insuficiencia hipofisaria se asocia a comorbilidades desfavorables en la evolución de la infección por coronavirus. Reportamos el primer caso de una mujer con hipopituitarismo e infección por coronavirus, destacando su evolución favorable, el posible rol de su tratamiento de base y el aporte de la telemedicina en el contexto epidemiológico actual.

Key concepts:

A)-What is already known on this subject?

Hypopituitarism has an increase in mortality rate, related to cardiovascular and cerebrovascular disease, both risk factors are known to be associated with the worst prognosis in patients diagnosed with COVID-19.

B)-What does this paper adds?

In face of the lack of scientific evidence in the management of patients with the pituitary disease during the COVID-19 pandemic, this case report adds our experience to collaborate on international knowledge. The use of telemedicine for the follow up of our patient is a plausible strategy for adequate patient treatment remotely.

Resumen:

Introducción: El nuevo coronavirus 2 del Síndrome Respiratorio Agudo Grave (SARS-CoV-2), la cepa viral que está causando la enfermedad pandémica conocida como COVID-19, está generando un desafío sin precedentes para los sistemas de salud de todo el mundo. Dicho escenario puede favorecer el deterioro de las patologías crónicas por la dificultad en el acceso al sistema sanitario. El hipopituitarismo es una condición clínica que se asocia a comorbilidades desfavorables en la evolución de la infección por coronavirus.

Objetivo: reportar el primer caso de infección por SARS-CoV-2 en una paciente con hipopituitarismo.

Métodos: se describe el primer caso de una mujer con insuficiencia hipofisaria e infección por SARS-CoV-2. Se destaca el aporte de la telemedicina como estrategia para seguir al paciente en forma remota.

Resultados: la paciente permaneció con el mismo esquema de terapia de reemplazo hormonal (eje tiroideo, gonadal y adrenal). Se implementó la telemedicina para asesorar sobre la adaptación del tratamiento. Debido a que cursó el proceso infeccioso en forma asintomática no se modificó la dosis de hidrocortisona, evidenciando una evolución favorable.

Conclusiones: los profesionales de la salud deben permanecer atentos y vigilar la evolución de los pacientes con insuficiencia hipofisaria e infección por SARS-CoV-2. El uso de la telemedicina, en pacientes seleccionados, se jerarquiza en el contexto epidemiológico actual.

Palabras claves: insuficiencia hipofisaria; coronavirus; telemedicina; corticoides.

Abstract:

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak originated in Wuhan (China) rapidly turned into a pandemic. Due to a national compulsive decree of quarantine, office visits for chronic disease control were delay.

Hypopituitarism includes all clinical conditions that result in partial or complete failure of the pituitary gland's ability to secrete hormones. Pituitary insufficiency *per se* has been associated with an increase in both morbidity and mortality, particularly due to cardiovascular disease, which is an important risk factor for COVID-19 disease severity.

Objective: To report the first case of SARS-CoV-2 infection in a patient with hypopituitarism, discuss the implications of the treatments the patient was taking and grade up the value of telemedicine in the present scenario.

Methods: Report of the clinical record of a patient with hypopituitarism and infection with SARS-CoV-2.

Results: During the span of the infection, the patient remained on the same hormonal therapeutic scheme (thyroid, gonadal and adrenal axis). The dose of hydrocortisone was not changed during the course of the infection as she was asymptomatic. We use telemedicine to control and advise her on the treatment.

Conclusion: Health care professionals should carefully follow up on the evolution of patients with hypopituitarism to provide them a safer outcome. The use of telemedicine as a methodology for selected patients acquires relevance in the present epidemiological context.

Keywords: hypopituitarism; covid-19; telemedicine; hydrocortisone

Resumo

Introdução: O novo coronavírus 2 da Síndrome Respiratória Aguda Grave (SARS-CoV-2), a cepa viral que está causando a doença pandêmica conhecida como COVID-19, está criando um desafio sem precedentes para os sistemas de saúde em todo o mundo. Esse cenário pode favorecer o agravamento das patologias crônicas devido à dificuldade de acesso ao sistema de saúde. O hipopituitarismo é uma condição clínica associada a comorbilidades desfavoráveis na evolução da infecção por coronavírus.

Objetivo: relatar o primeiro caso de infecção por SARS-CoV-2 em paciente com hipopituitarismo.

Métodos: é descrito o primeiro caso de uma mulher com insuficiência hipofisária e infecção por SARS-CoV-2. A contribuição da telemedicina é destacada como estratégia para acompanhar o paciente à distância.

Resultados: a paciente permaneceu com o mesmo esquema de terapia de reposição hormonal (eixo tireoidiano, gonadal e adrenal). A telemedicina foi implantada para orientar sobre a adaptação do tratamento. Devido ao processo infeccioso assintomático, a dose de hidrocortisona não foi modificada, apresentando evolução favorável.

Conclusões: os profissionais de saúde devem permanecer vigilantes e acompanhar a evolução dos pacientes com insuficiência hipofisária e infecção por SARS-CoV-2. O uso da telemedicina, em pacientes selecionados, é hierárquico no contexto epidemiológico atual.

Palavras-chave: insuficiência pituitária; coronavírus; telemedicina; corticosteróides

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Background

On 31st December 2019, the Wuhan's Health Town Hall Commission (Hubei, province of China) notified a cluster of pneumonia in the city. A few days later it was determined that those were caused by the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), resulting in the disease known as COVID-19 (1).

Due to its rapid progression around the world, on 11th March 2020, the World Health Organization declared it a pandemic (2). Since then, the world scientific community has gathered efforts to find a cure for the disease that spreads worldwide with millions of people affected.

In the present scenario, strategies developed from different health services vary according to the affected country. As a strategy to face the emergency, the control of chronic diseases is delayed and pituitary disorders are not the exception (3).

Hypopituitarism or pituitary insufficiency includes all clinical conditions that result in partial or complete failure of the anterior and rarely of the posterior lobe of the pituitary gland to secrete hormones. It may be due to a pituitary or hypothalamic dysfunction caused by acquired or less frequently a genetic origin. Pituitary tumors or the complications of its treatment (surgery or radiotherapy) are the most frequent etiology. Extra pituitary tumors can induce hypopituitarism, and craniopharyngioma is the most frequent etiology of suprasellar masses (4). The objective of this case report is to present the first case of SARS-CoV-2 infection in a patient with hypopituitarism, emphasizing its uneventful outcome, discuss the influence of the medications she was taking, and that follow up underwent through telemedicine due to pandemics.

Case

We present a 39-year-old woman, nulliparous, from the province of Santa Fe, Argentina. Her clinical record showed a craniopharyngioma diagnosed when she was 16 years old, treated with many surgeries (2 transcranial and 4 transsphenoidal), and radiotherapy due to tumor recurrence. As a sequel, she presents right eye amauroses, left eye temporal hemianopia, and hypopituitarism. Her pituitary hormonal deficit requires the following replacing therapy: hydrocortisone 25 mg, levothyroxine 125 µg, ethinylestradiol 0.02 mg, and gestodene 0.075 mg daily. She is also diagnosed with secondary osteoporosis receiving treatment with calcium citrate 1500 mg/day and vitamin D3 100,000 IU every 3 months and ibandronate 150 mg/month. Hypercholesterolemia is under treatment with rosuvastatin 10 mg/day and lifestyle measures. Her treatment adherence remains optimal, having had stable medical controls over the last 10 years.

In December 2019 she had a clinical, laboratory, and magnetic resonance image control. On physical examination she was overweight (74 kg, 1.64 m height and BMI 27.5 kg/m², waist circumference 100 cm), blood pressure 120 / 70 mmHg without orthostatic hypotension, and 80 beats per minute. Thyroid palpation was normal, galactorrhea was not found, she had poor axillary and pubic hair and normal tendon reflexes. Laboratory findings are depicted in Table 1. Magnetic resonance image centered in the pituitary show a tumor remnant of 1 cm in diameter in parasellar left region (hyperintense in T2 and isointense in T1 without enhancement with gadolinium), pituitary gland was flattened. No changes were seen in the last 6 years.

On 24th March 2020, her husband, a 38-year-old man was diagnosed with COVID-19 disease, corresponding to the first outbreak in the city. As a close contact, she was tested with nasopharyngeal swab and it was analyzed with rtPCR for SARS-CoV-2 at Carlos G. Malbrán Institute (Buenos Aires, Argentina) showing a positive result. As the patient had no fever or respiratory symptoms she was instructed to self-isolate at home, receiving clinical control through telemedicine.

As the whole country was under an enforced "lockdowns" (decree of necessity and urgency - DNU 2020-297) non-urgent medical

visits were forbidden, so endocrinologist visits were carried out through telemedicine. She was advised to continue with the same doses of hormonal replacement therapy (thyroid, gonadal, and adrenal axis) addressing alarm guidelines about dose adjustments in case of fever or respiratory symptoms. Weekly video calls were scheduled with the endocrinologist to control daily temperature records (3 a day) or respiratory symptoms known for SARS-CoV-2 infection. During the consultation, the interrogation was guided to address suggestive symptoms of adrenal insufficiency like myalgia, asthenia, fatigue, loss of appetite, weight loss, nausea, vomiting, dizziness, orthostatic symptoms, and others. The patient remained asymptomatic during all the evolution of the disease, having a negative rtPCR swab 30 days after the diagnosis.

Table 1: Biochemical endocrine and metabolic profile.

Biochemical profile	Value	Normal values
Fasting Glycemia	88 mg/dL	70 – 100 mg/dL
Blood urea	40 mg/dL	15 – 45 mg/dL
Serum Creatinine	0.9 mg/dL	0.5 – 1.1 mg/dL
Serum Calcium	8.9 mg/L	8.5 – 10.5 mg/L
Serum Phosphorous	3.15 mg/dL	2.5 – 4.5 mg/dL
Serum 25(OH) D	35 ng/mL	>30 ng/ml
Total cholesterol	214 mg/dL	< 200 mg/dL
HDL cholesterol	56 mg/dL	> 50 mg/dL
LDL cholesterol	125 mg/dL	< 130 mg/dL
Triglycerides	162 mg/dL	< 150 mg/dL
Serum Sodium	142 mEq/L	135 – 145 mEq/L
Serum Potassium	4 mEq/L	3.5 – 5.5 mEq/L
Luteinizing hormone	0.15 µUI/ml	1.8 – 11.8 µUI/ml
Follicle stimulant hormone	0.62 µUI/ml	3.9 – 10 µUI/ml
Estradiol	36 pg/mL	21 – 251 pg/mL
TSH	0.01 µUI/ml	0.4 – 4 µUI/ml
FT4	1.4 ng/dL	0.8 – 1.9 ng/dL
PRL	8.9 ng/dL	5 – 25 ng/dL
IGF-1	< 25 ng/mL	177 – 385 ng/mL
UFC	61 µg/24 hours	21 – 110 µg/24 hours

Abbreviations: 25(OH) D:25- Hydroxyvitamin D; LH: luteinizing hormone; FSH: follicular-stimulating hormone; TSH: thyroid-stimulating hormone; FT4: free T4; PRL: prolactin; IGF-1: insulin-like growth factor; UFC: 24- h urinary free cortisol.

Discussion

In face of restrictions imposed by the government, telemedicine emerged as a strategy aiming to facilitate the control of chronic pathologies, advising on medication changes as in any other medical condition that could be assessed remotely (3, 5).

Derangements over the endocrine system caused by SARS-CoV-2 remain unexplored. Many observations published during the previous outbreak of SARS (2003) on the effects over the endocrine system might be extrapolated to SARS-CoV-2, however, there is no present evidence to confirm this statement (6, 7).

Clinical manifestations of hypopituitarism depend on the causing etiology (mass effect from tumoral causes) and the severity and number of compromised hormonal axis. Treatment of the adrenal axis is critical (secondary adrenal insufficiency) because the occurrence of an infectious disease could rapidly develop an acute adrenal crisis leading to death if not promptly diagnosed and treated. Doubling the usual corticosteroid dose in the face of the first signs of disease, the reassurance of parenteral corticosteroids supply, and having an identification card are mandatory for every patient with adrenal insufficiency (8). The patient was on 25 mg/day of hydrocortisone, 2/3 in the morning, and 1/3 in the afternoon, trying to resemble cortisol circadian rhythm. Because the patient did not have a fever and remained asymptomatic the dose of hydrocortisone was not increased. That conduct was possible to be carried out since the patient and her family had adequate knowledge of the disease, alarm sign and for the close contact (*online*) with her treating physicians.

Mortality rates are increased amongst patients with hypopituitarism, linked to cardiovascular and cerebrovascular diseases; both of them considered important risk factors for the worst evolution in patients with COVID-19 disease (3). Even more, patients with adrenal insufficiency have increased mortality due to respiratory infections, possibly explained for derangement of the immune system. The opposite, excessive dosing of glucocorticoids for replacement, is also deleterious because induces immunosuppression (8). An accurate balance in the treatment of adrenal insufficiency is mandatory during the pandemic.

Hypopituitarism and overweight that our patient suffered precluded a severe outcome. Possible explanations for her uneventful outcome could be her young age and the treatments she was taking.

One of the tactics of the virus to elude the host immune system, as the influenza virus too, is to block the host's cortisol response to stress. An interesting hypothesis is that SARS-CoV expresses a certain sequence of amino acids that possess a molecular homology with adrenocorticotrophic hormone (ACTH). This kind of molecular mimicry could block stress-induced cortisol host's response through the presence of antibodies against ACTH (9). As SARS-CoV and SARS-CoV-2 share 90 to 99 % homology in its proteins, emerges the hypothesis if this new virus could use the same strategy too. In that hypothetical event, our patient treated with exogenous corticosteroids and ACTH deficit could have been protected from this pathogenic mechanism. Nevertheless, present data suggest that offering corticosteroids to patients that don't need respiratory aid offers no benefit (10).

Despite the somatotrophic deficit was related to derangements in life quality and greater cardiovascular risk, our patient was not replaced with this hormone for the possible worsening of the craniopharyngioma remnant (4).

Low plasma vitamin D levels have been associated with a poorer outcome with COVID-19 infection. The proposed mechanism for which vitamin D could protect from viral infection includes: reducing viral replication through the synthesis of cathelicidins, maintaining tight gap junctions in endothelial cells, and reducing concentrations of pro-inflammatory cytokines like tumor necrosis factor α and interferon γ (11).

The favorable course that our patient had might also be due to she was treated with vitamin D and reached optimal plasma levels. Nevertheless, other findings from a large database study in the United Kingdom couldn't find this protective association (12).

The protecting effect of statins, which our patient was taking, is under debate too (13). A dramatic improvement was seen in patients that received rosuvastatin when infected from Ebola, another RNA virus that causes extensive endothelial damage through cytokine dysregulation as SARS-CoV-2 do (14). Use of statins during influenza virus infection was associated with lower lung injury scores and a reduction of severity of illness, but there is no published information yet comparing the evolution of the disease according to the use or not of statins in SARS-CoV-2 infected patients (15).

Conclusion

Health care professionals should carefully follow up on the evolution of patients with hypopituitarism to provide them a safer outcome. The use of telemedicine methodology for select patients acquires relevance in the present epidemiological context.

Limitaciones de responsabilidad

La responsabilidad del trabajo es sólo de los autores

Conflictos de interés

Ninguno

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Originalidad del trabajo

Este artículo es original y no ha sido enviado para su publicación a otro medio de difusión científica en forma completa ni parcialmente.

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Participación de los autores

Todos los autores hemos participado en la concepción del diseño, recolección de la información y elaboración del manuscrito, haciéndose públicamente responsables de su contenido y aprobando su versión final.

Bibliography

- 1-Wu Z, McGoogan JM. Characteristics of and 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. doi:10.1001/jama.2020.2648
- 2-WHO announces COVID-19 outbreak a pandemic. In: <http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/whoannounces-covid-19-outbreak-a-pandemic>; Downloaded: April 2020
- 3-Fleseriu M, Buchfelder M, Cetas JS, Fazeli PK, Mallea-Gil SM, Gurnell M, et al. Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic-an international perspective. *Pituitary* 2020; 23:327-337
- 4-Higham CE, Johannsson G, Shalet SM. Hypopituitarism. *Lancet* 2016; 388: 2403-2415
- 5-Rockwell KL, Alexis S. GilroyA. Incorporating Telemedicine as Part of COVID-19 Outbreak Response Systems. *Am J Manag Care*. 2020;26(4):147-148

- 6-Mongioli L, Barbagallo F, Rosita A, Condorelli R, Cannarella R, Aversa A, et al. Possible long-term endocrine-metabolic complications in COVID-19: lesson from the SARS model. *Endocrine*. 2020; 68 (3): 467-470
- 7- Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *J Endocrinol Invest*. 2020; 43 (7): 1027-1031
- 8-Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. [Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline](#). *J Clin Endocrinol Metab*. 2016; 101 (11):3888-3921
- 9-Wheatland R, Molecular mimicry of ACTH in SARS-implications for corticosteroid treatment and prophylaxis. *Med. Hypoth*. 2004; 63: 855-862
- 10- RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*. 2020 Jul 17. doi: 10.1056/NEJMoa2021436
- 11- Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL et al. Evidence that vitamin D supplementation could reduce the risk of influenza and COVID-19 infections and death. *Nutrients* 2020;12: 988
- 12- Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr* 2020;14: 561-565 doi: 10.1016/j.dsx.2020.04.050. Epub 2020 May 7
- 13- Castiglione V, Chiriaco M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother* 2020;6: 258-259 doi:10.1093/ehjcvp/pvaa042
- 14- Fedson DS, Rordam OM. Treating Ebola patients: a "bottom up" approach using generic statins and angiotensin receptor blockers. *Int J Inf Diseases* 2015;36: 80-84
- 15- Fedson D, Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antivir Res* 2013; 99:417-435