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SCIENTIFIC LETTER

Anti-ACTH antibodies in critically ill Covid-19 patients: A potential immune evasion mechanism of SARS-CoV-2

Anticuerpos anti-ACTH en pacientes críticos con Covid-19: Un posible mecanismo de evasión inmunitaria del SARS-CoV-2

Dear Editor,

Coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high morbimortality worldwide. SARS-CoV-2 exhibits a great number of mechanisms to evade the immune response, including suppression of the host's cortisol stress response.[1] Several potential mechanisms for adrenal insufficiency (AI) have been proposed.[2] One of them is based on the expression of amino acid sequences by SARS-CoV-2 that are remarkably similar to those of the host adrenocorticotropic hormone (ACTH).[1,3] Production of antibodies against viral antigens may also lead to destruction of the host ACTH, avoiding the increase of cortisol and resulting in a relative AI. However, there is little data on the evidence of the existence of anti-ACTH antibodies and on the levels of cortisol in Covid-19 patients.[1,3]

We performed a proof-of-concept study to assess whether anti-ACTH antibodies were detectable in critically ill Covid-19 patients. We measured plasma levels of cortisol and ACTH as exploratory variables. The study was approved by the Institutional Ethics Review Board. Informed consent was obtained from the patient or representative prior to enrollment.

All the Covid-19 patients undergoing mechanical ventilation (MV) admitted to the Intensive Care Unit (ICU) of our University Hospital within a 10-week period (January to March 2021) were eligible to participate. Inclusion criteria were: (1) SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) in a nasopharyngeal swab or bronchoalveolar lavage specimen; (2) Development of at least two signs or symptoms of AI: hyponatremia, hyperkaliemia, lymphopenia, eosinophilia, hemodynamic instability and/or hyperthermia; and (3) The signs or symptoms of AI were not straightforwardly explained by alternative confounders (i.e. infection/sepsis, pulmonary embolism, diuretics, etc.). The only exclusion criterion was unwillingness to give informed consent. Measurements were also performed in a control group of patients admitted to the hospital ward for acute respiratory failure for reasons other than Covid-19, without suspected AI, and Addison's disease patients from the outpatient clinic, all of them within the recruitment period.

A total of 40 Covid-19 patients were admitted during the recruitment period: age 60 ± 14, 73% male, APACHE-II 15 (11–20), 87.5% underwent MV, length of MV 21 (8–30) days, ICU length of stay (LOS) 16 (9–37) days, hospital LOS 38 (21–65) days, hospital mortality 10%. A total of 10 (25%) patients met inclusion criteria: age 61 ± 19, 67% male, APACHE-II 19 (15–21), 100% underwent MV, length of MV 46 (25–68) days, ICU LOS 69 (43–72) days, hospital LOS 78 (63–110) days, hospital mortality 20%.

We measured specific anti-ACTH IgE-class antibodies (ImmunoCAP™ IgE assays, Thermo Fisher Scientific/Phadia, Uppsala, Sweden), and plasma levels of cortisol and ACTH, at the moment when inclusion criteria were fulfilled (Table 1). We found specific anti-ACTH IgE-class antibodies in 60% of Covid-19 patients with suspected AI, half of them together with low levels of plasma cortisol and ACTH. Note 70% of the patients were receiving corticosteroids at the time of assessment (Table 1, Electronic Supplementary Material). We did not find detectable titers of these antibodies in controls.

Corticosteroids have become the standard of care in critically ill Covid-19 patients undergoing MV, after demonstrating a survival benefit.[4] However, the underlying mechanism explaining this phenomenon has not been elucidated yet. The inflammatory profile orchestrated by T helper cells (Th) in severely ill Covid-19 patients supports the predominance of a Th2 polarization, which primarily activates a humoral response, via interleukins 4 and 6.[5–7] This response has been linked to a dysregulated cytokine release or ''cytokine storm'', and has been associated with poor prognosis.[6] The reason why we decided to measure specific IgE-class antibodies is that the Th2 pathway is involved in allergen-specific and related IgE-based events, since IL-4 induces production of these antibodies by B cells.[5,7] We found a 60% prevalence of anti-ACTH IgE-class antibodies in patients with suspected AI. Levels of plasma ACTH were low in 4 out of 6 patients, with a plausible contribution of anti-ACTH IgE-class antibodies. A partial explanation by negative feedback from exogenous administration of corticosteroids is feasible in 3 out of 4 patients, but not in the remaining. We observed 2 out of 4 patients without anti-ACTH IgE-class antibodies exhibited low levels of plasma cortisol and ACTH, suggesting either exogenous administration of corticosteroids, or implication of other potential mechanisms of AI in Covid-19 patients, like the negative feedback toward the hypothalamic-pituitary-adrenal axis provided by the immune dysregulation caused by SARS-CoV-2, or the

Table 1 Clinical characteristics of the patients, anti-ACTH IgE, cortisol and ACTH levels.

Patient	Age	Sex	APACHE-II	Covid-19	Atopy	Lymphocyte count, $\times 10^3/\mu L$ (0.8–5)	Eosinophil count, $\times 10^3/\mu L$ (0.1–0.65)	Sodium, mmol/L (136–146)	Potassium, mmol/L (3.5 – 5.1)	Hemodynamic instability	Hyperthermia	Anti-ACTH IgE, KU/L (<0.10)	Cortisol, μg/dL (6.7–22.6)	ACTH, pg/mL (5–46)	Corticosteroids at the time of assessment?	Days from admission to assessment
1	56	M	13	Yes	Yes	**0.7**	**2.3**	**135**	4.4	No	**Yes**	**12.9**	**1.1**	**<5**	Yes	33
2	67	M	21	Yes	Yes	**0.5**	0.1	**133**	4.9	**Yes**	**Yes**	**0.19**	**6.1**	**<5**	Yes	61
3	79	F	21	Yes	No	1.3	1.4	**131**	**5.2**	**Yes**	No	<0.10	15.5	16	Yes	24
4	76	M	20	Yes	No	**0.2**	0.4	**130**	5	**Yes**	No	**0.82**	8.9	**<5**	No	20
5	67	F	18	Yes	Yes	**0.4**	1.7	**127**	4.9	No	No	<0.10	**1.8**	**<5**	Yes	38
6	68	M	12	Yes	No	**0.4**	0.9	**132**	**6**	No	**Yes**	**9.01**	15.4	5.6	No	34
7	70	M	16	Yes	No	**0.3**	0.6	**133**	4.8	No	**Yes**	<0.10	12.1	**<5**	Yes	63
8	78	F	24	Yes	No	**0.5**	0.1	137	**5.8**	No	No	**21**	**1.8**	**<5**	Yes	18
9	24	M	20	Yes	No	**0**	**1**	**129**	4.8	No	No	**0.62**	16.81	17.7	No	23
10	70	M	15	Yes	No	**0.6**	**1**	**132**	4.7	No	No	<0.10	**2.32**	**<5**	Yes	22
C1	64	M	5	No	No	1.6	0.1	142	4	No	No	<0.10	15.2	16	No	6
C2	70	F	7	No	Yes	1.9	**0.7**	146	3.8	No	No	<0.10	16.1	29.7	No	5
C3	82	M	8	No	No	1.5	0.4	140	4.1	No	No	<0.10	18	19	No	7
C4	59	F	7	No	Yes	1.9	0.6	139	3.9	No	No	<0.10	12.8	22.4	No	6
C5	67	M	7	No	No	1.9	0.1	142	4.2	No	No	<0.10	13.1	17.6	No	7
C6	90	M	10	No	Yes	2.3	0.6	141	3.7	No	No	<0.10	12.5	19.2	No	5
C7	75	F	10	No	No	3.6	0.1	139	3.9	No	No	<0.10	15.3	21	No	4
C8	75	M	8	No	No	1.4	0.2	145	4.1	No	No	<0.10	16.2	18.9	No	8
C9	80	M	10	No	No	1.9	0.1	140	4.2	No	No	<0.10	14.3	12.3	No	7
C10	91	M	12	No	No	1.5	0.3	141	4.4	No	No	<0.10	15.4	40.1	No	6
A1	56	F	6	No	No	1.4	**0.7**	**126**	**5.6**	No	No	<0.10	**1.2**	**50**	Yes	–
A2	78	F	10	No	No	1	**0.8**	**130**	5	No	No	<0.10	**1.9**	**150**	Yes	–
A3	62	F	4	No	No	1	**0.7**	138	**5.4**	No	No	<0.10	**7.3**	**150**	Yes	–

Normal reference limits are described in parentheses. In bold, levels outside the reference ranges. Note laboratory data in Covid-19 patients represent the greatest deviation during the ICU stay (lowest value of lymphocyte count and sodium, and highest value of eosinophil count and potassium). C = controls, A = Addison's disease patients. Anti-ACTH IgE levels: <0.10 KU/L, negative; 0.10–1.9 KU/L, mildly elevated; 2–14.9 KU/L, moderately elevated; >15 KU/L, highly elevated.

entrance of the virus in the glands through the angiotensin-converting enzyme 2, causing hypophysitis and adrenalitis.[2]

Our study has some limitations. First, we only included Covid-19 patients with suspected AI, since anti-ACTH antibodies were expected to reduce ACTH levels, leading to a decrease in cortisol. This aimed to maximize the probability to demonstrate the existence of anti-ACTH antibodies, but may reduce generalizability. Second, although inclusion criteria required at least two signs or symptoms of AI that were not straightforwardly explained by alternative confounders, these signs remain to be highly unspecific. Inclusion of patients without suspected AI would allow to assess the prevalence of anti-ACTH antibodies more accurately. Third, we were unable to recruit a control group of non-Covid-19 critically ill patients, since ICU occupancy rate by Covid-19 patients was close to 100% during the study period. A matched control group would be desirable in the future. Fourth, although anti-ACTH IgE-class antibodies were detected, our study did not assess other immunoglobulin classes, which would merit further exploration. Fifth, exogenous administration of corticosteroids at the moment of inclusion limits the interpretation of ACTH and cortisol levels. Last, the inherent limitations of a proof-of-concept study, including single center design and small sample size.

To our knowledge, this is the first time that anti-ACTH antibodies have been described in severely ill Covid-19 patients. We suggest SARS-CoV-2 may take advantage of its homology with human ACTH to evade the host immune system by blocking the primary immune response and blunting the natural response of the hypothalamic-pituitary-adrenal axis to stress, leading to a relative AI state. We believe anti-ACTH antibodies play a plausible role in the pathophysiology of severe Covid-19, which may have potential clinical implications and merits further research.

Author's contributions

David Pérez-Torres and Cristina-Díaz Rodríguez contributed to the design of the work, sample acquisition (Covid-19 population), data acquisition, interpretation of data for the work, drafting the work and revising it critically for important intellectual content. Alicia Armentia-Medina contributed to the conception and design of the work, sample acquisition (control population), data acquisition, analysis of the samples, interpretation of data for the work, drafting the work and revising it critically for important intellectual content. All the authors approved the final version of the manuscript to be published.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medin.2021.09.002.

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