ISSN: 2455 – 9938
PubMed- National Library of Medicine - ID: 101731611

EIJO: Journal of Science, Technology and Innovative Research (EIJO–JSTIR)
Einstein International Journal Organization (EIJO)
Available Online at:www.eijo.in
Volume – 7, Issue – 2, March - April - 2022, Page No. : 23 - 29

Hypocortisolism in survivors of severe acute respiratory syndrome (SARS)

[1]Dr.Bhagwan Mantri, DNB (Pulmonary Medicine), IDCCM (Critical Care), Consultant Pulmonologist, Moolchand Hospital,Delhi

[2]Dr. Pankaj Gulati, MBBS,DNB, IDCCM, Consultant Pulmonologist, Sahilby Hospital Jaipur

[3]Dr. Ashish Ranjan, Specialist chest physician, National Institute of TB and RD

[4]Dr. Ashok Shukla, MBBS, MD (TB & Chest), (Ex. CMO), Assistant Professor, Respiratory Medicine, Rama Medical College & Hospital,Kanpur.

Corresponding Author: Dr. Bhagwan Mantri, DNB (Pulmonary Medicine), IDCCM (Critical Care), Consultant Pulmonologist, Moolchand Hospital, Delhi

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Many survivors of the severe acute respiratory syndrome (SARS) were found to have psychosomatic symptoms that were similar to endocrine abnormalities. As a result, we wanted to see if there were any persistent endocrine sequelae in SARS survivors.

Patients, design, and measurements: Three months after recovery, sixty-one SARS survivors were prospectively recruited and tested for hormonal imbalances. Patients with endocrine problems were not allowed to participate. Up to a year, any endocrine problems discovered were evaluated and treated as needed. Serial examination aided in the identification of trends and the prognosis of any endocrinological abnormalities.

Results Twenty-four patients (39.3%) showed signs of hypocortisolism. The majority of patients' hypothalamic–pituitary–adrenal (HPA) axis abnormalities resolved within a year. Transient subclinical thyrotoxicosis was found in two (33% of the hypocortisolic group). Four (67%) of the participants were biochemically hypothyroid, with three having central hypothyroidism and one having primary hypothyroidism. Two of the three had central hypothyroidism and central hypocortisolism at the same time. Eight of the participants had DHEAS levels that were below normal.

Conclusions: These preliminary data suggest that SARS-associated coronavirus may have a role in generating reversible hypophysitis or a direct hypothalamic effect, with the HPA axis being affected more frequently than the HPT axis.

Keywords: Hypothalamic–Pituitary–Adrenal, Hypophysitis, Central Hypothyroidism

Introduction

Since the outbreak of severe acute respiratory syndrome (SARS-CoV2) in China in Dec 2019, it has become clear that many survivors have suffered from persistent pulmonary morbidities as well as a variety of psychological symptoms.

Due to their similarities to numerous hormonal and metabolic illnesses that typically show nonspecific symptomatology, we propose that some of these extrapulmonary symptoms have an endocrinological origin.

1. Abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis have been related to psychiatric conditions in studies.
2. In addition, several psychosomatic illnesses have been linked to hypothalamo–pituitary–thyroid (HPT) axis dysfunction.
3. The primary goal of this prospective study is to see if SARS survivors have any chronic HPA axis sequelae, as well as to characterise their prognostic outcomes and see if they have any HPT axis dysfunction.

Given that the endocrinopathic properties of the SARS-associated coronavirus (SARS-CoV) are currently understudied, any hormonal abnormalities discovered through this preliminary investigation will add to the medical database and have the potential to translate into clinically relevant therapeutic strategies for SARS-associated endocrinopathies.

Patients and procedures

Recruitment of subjects

A total of 238 people were infected with SARS, with 33 of them dying. The study was done at Moolchand hospital, Delhi. All SARS survivors who were 21 years old or older were eligible. Those who had endocrine abnormalities prior to SARS were not eligible.

Two patients with underlying primary hypothyroidism were excluded from the study, and 61 patients who met the inclusion criteria and provided written informed consent were prospectively enrolled about 3 months after discharge, with the last batch of patients entering the study on September 30, 2020, and followed until October 1, 2021. The majority of the remaining survivors who were not recruited declined for a variety of personal reasons, including inconvenience, incapacity to be followed up for a year, or their aversion to being subjected to laboratory testing. A number of survivors declined to participate because they were either psychologically unprepared or in a state of mourning over their loved ones who had died.Some remained unreachable and could not be recruited, while many were minor participants who were not included in the study. Using the intensive care unit (ICU) as an arbitrary criterion for severe SARS, 46 severe SARS cases were admitted to the ICU, of which 20 survived; eight severe SARS subjects were enrolled, while 12 declined. As a result, 131% (8/61) of the survivors with severe SARS were recruited, while 83 percent (12/144) were not. As a result, the study cohort included more people with severe SARS than those who were not enrolled in the trial.Collection of samples and methodology

At 0800 h, blood samples were drawn into EDTA and plain tubes for the following tests: 1) whole blood count, 2) electrolytes, 3) cortisol, 4) ACTH, 5) free T4, 6) free T3, 7) TSH, and 8) dehydroepiandrosterone sulphate (DHEAS). Urinary free cortisol (UFC) was measured over 24 hours to determine integrated cortisol secretion. Subjects with blood cortisol levels below 275 nmol/l were given a low dose (1 g) Synacthen (ACTH-1- 24) test to assess the dynamic HPA axis (SST). Hypocortisolic subjects had blood cortisol levels of less than 138 nmol/l at 0800 h and/or less than 550 nmol/l at 30 min after stimulation. SST evaluations for HPA axis recovery were done every three to six months. Despite the fact that the trial concluded after one year, participants with persistent hypocortisolism had their reviews prolonged as medically necessary. Physiological doses of hydrocortisone replacement were provided to symptomatic individuals with orthostatic hypotension until their SST corrected.Determinations based on biochemistry and immunoassays

The blood was centrifuged the plasma was separated, frozen, and kept at 30°C until testing. Hormone measuring techniques such as immunochemiluminometric assay (ICMA), radioimmunoassay (RIA), and immunoradiometric assay (IRMA) were used in accordance with established manufacturers' protocols, with detection limits, intra- and interassay **coefficients of variation included in the package.**

Analytical statistics

Where applicable, descriptive statistical analysis was done on raw data. The nonparametric Wilcoxon signed ranks test was used to evaluate paired numerical data for stimulated cortisol end-points at successive evaluations. To demonstrate statistical significance, a two-tailed P value of 005 or less was employed as a criteria. On a personal computer (version 120), the analysis was carried out using the sss statistical software package.

Approval on ethical grounds

The study was authorised by the institutional review board (Research and Ethics Committee) since it followed existing good clinical practice recommendations and complied with the Declaration of Helsinki4.

Results

The demographic and clinical profile of the study population is shown in Table 1. Twenty-four patients (39.33%) exhibited hypocortisolism, with 20 (83.33%) having clear central hypocortisolism as evidenced by low or abnormally normal ACTH levels (Table 2). Four (16.7%) of the participants showed hypocortisolism due to plasma ACTH levels exceeding the upper reference range of 11 pmol/l (50 pg/ml). Although the levels of ACTH were high enough to suggest primary hypocortisolism, they were not high enough to be diagnostic of primary hypocortisolism. Primary care is used in the absence of renin–aldosterone data and overt addisonian crises.Primary adrenal insufficiency was improbable given the lack of renin–aldosterone data and overt addisonian crisis, but secondary hypocortisolism appears to be the most common form of HPA axis dysfunction seen here. Indeed, the increased ACTH could be a sign of the HPA axis regaining function after steroid suppression. Among these four patients, the one who was given systemic steroids during SARS was most likely a case of central hypocortisolism rather than primary hypocortisolism, having been recruited at a time when the hypothalamo-pituitary unit was recovering from transient HPA axis suppression, while the other three with elevated ACTH who had no steroids exposure during SARS or prior to SARS could arguably be cases of SARS-induced central hypocortisolism showing evidence ofearly hypothalamo-pituitary recovery rather than primary adrenal insufficiency.

Variable	Value
Age	36.5 (25.5 - 47.5)
Gender (Male: Female)	14:47
Use of corticosteroids during SARS	10
Number who required ICU care	8
Mechanical ventilation	7
Need for tracheostomy	3

Table1: Clinical characteristics of the study population (n= 61)

Patient			0 min	30 min	0 min	30 min	0 min	30 min
	(NR:2–11)	(NR:59–413)						
1	4·3	42	108	174	170	582	–	–
2	11·6	160	259	307	253	504	Default	–
3	16·9	106	368	391	322	588	–	–
4	3·0	118	58	207	269	649	–	–
5	4·6	Not done	214	279	188	485	Default	–
6	2·9	200	159	244	216	720	–	–
7	2·3	Not done	254	272	213	586	–	–
8	18·7	56	90	443	106	469	Default	–
9	3·7	150	225	262	251	708	–	–
10	3·2	Not done	146	273	190	528	Default	–
11	3·9	128	104	133	220	579	–	–
12	6·1	173	279	299	519	760	–	–
13	6·1	Not done	181	189	268	652	–	–
14	2·3	73	201	384	274	363	223	537
15	7·4	24	90	205	171	483	526	575
16	6·4	84	191	225	174	310	131	662
17	2·0	102	93	117	167	234	196	676
18	3·9	139	201	222	262	299	108	554
19	7·3	76	280	322	441	455	565	750
20	4·6	13	165	240	226	309	182	678
21	16·9	133	130	151	294	305	185	255

24h UFC S ST1: F (n mol /l) n=21SS T2: F (n mol/l) n=21SS T3: F (n mol/l) n=8

Table 2: SST1, SST2 and SST3 represent these quintal order (i.e.1st, 2nd, and 3rd) of the low dose short Sync then test being per formed during the follow-up of hypocortisolic patients. Wilcoxon signed ranked test on 30 min F between SST1 and SST2 revealed a statistically significant improvement in stimulated serum cortisol's over time(P<0•001).(Abbrev: Fis serum cortisol, UFC is urinary free cortisol, NR is normal range, while n is the number of patients)

Patient	Plasma Cortisol (n mol / l)	Plasma Cortisol 0 min (n mol/l)	30 min.	Plasma Cortisol (n mol/ l) 60 min
A	1220	1640		–
B	619	1190		1410
C	>1700	>1700		–
D	683	1440		1700
E	877	1310		–
F	182	643		–
G	1060	1340		–
H	354	828		–
I	664	1100		–
J	633	660		691
K	880	1500		1600
L	1330	1420		–
M	702	1070		1250
N	1650	>1700		–
O	558	858		–

Table 3: Baseline and stimulated plasma cortisols of 15 critically ill SARS patients (eight of whom survived and participated in our study) prior to parenteral glucocorticoid therapy

Discussion

SARS is a unique infection with high morbidity and fatality rates that poses a serious threat to humanity in the new millennium.5 During clinical follow-up, survivors of SARS experienced a cluster of chronic extrapulmonary symptoms including lethargy, malaise, lassitude, fatigue, weakness, orthostatic dizziness, anorexia, apathy, anxiety, and melancholy. These symptoms were similar to those reported in a variety of endocrine illnesses, including hypothyroidism, hypocortisolism, thyrotoxicosis, hypercalcaemia, hypopituitarism, and Cushing's syndrome, despite being generally vague, ambiguous, and ill-defined. During the viraemic phase, this coronavirus might theoretically infect any organ. Because viral aetiologies can induce hypophysitis, thyroiditis, and adrenalitis,6–8 it's important to figure out how SARS-CoV affects the endocrinology. Researchers have recently looked into the pulmonary and psychological effects of SARS survivors. 9,10 However, the majority of investigations were cross-sectional with minimal longitudinal data, and no endocrine abnormalities have been documented to our knowledge.

For up to a year, our inquiry documented an unparalleled effort to track the natural history of endocrine dysfunction, particularly that of the HPA axis, in SARS survivors. The ability to characterise patterns and predict outcomes was aided by serial longitudinal examination. Surprisingly, cortisol deficiency was found in a significant number of people, rather than the up-regulated HPA axis or thyroid status seen in depression and panic disorder. 11–13 The cortisol disturbances

seen here are similar to those seen in chronic fatigue syndrome, post-traumatic stress disorder, and primary fibromyalgia syndrome, in which the HPA axis appears to be disrupted.14,15

The absence of steroid use in approximately two-thirds of this cohort indicates central hypocortisolism caused by a pathogenic impact of SARS rather than glucocorticoid-induced HPA axis suppression. Furthermore, those who had a normal reaction to the low-dose SST despite having taken high-dose glucocorticoids support the glucocorticoid regimen's temporary and minimally suppressive effect on the HPA axis. Taken together, this suggests that HPA axis dysfunction is more likely a delayed pathological complication of SARS than a result of exogenous steroid suppression. Apart from a moderate reduction in MAP during SARS-related pyrexia, the absence of overt hypotension during the acute febrile phase of SARS in survivors who developed hypocortisolism later also shows that SARS-related hypocortisolism is caused by SARS.Evidence from those who had an undamaged HPA axis by standard dosage SST during acute SARS but had an impaired HPA axis by low dose SST three months later backs this up.

Despite being speculative, the overall data are consistent with the concept that hypocortisolism develops gradually as a late consequence in SARS survivors some weeks after infection. Because the majority of these patients were young (mean age 365), previously healthy, and had no prior corticosteroid exposure, the SARS-CoV is a compelling candidate for being the aetiologic agent causing hypocortisolism.

Conclusion

Overall, the data point to SARS causing reversible hypophysitis or a direct hypothalamic effect, with the HPA axis being more frequently disrupted in SARS survivors than the HPT axis. These findings, albeit speculative, point to a putative aetiologic involvement of SARS-CoV as an endocrinopathic component that deserves further investigation through in vitro, animal, and clinical research.

References

1. Frohman, L.A. &Felig, P. (2001) The clinical manifestations of endocrine disease. In: P. Felig, L.A. Frohman eds. Endocrinology and Metabolism, 4th edn. McGraw-Hill, New York, 19 – 28.
2. Kathol, R.G., Noyes, R. & Lopez, A. (1988) Similarities in hypothalamic– pituitary–adrenal axis activity between patients with panic disorder and those experiencing external stress. Psychiatric Clinics of North America, 11, 335 – 348.
3. Kjellman, B.F., Thorell, L.H., Orhagen, T., d'Elia, G. &Kagedal, B. (1993) The hypothalamic–pituitary–thyroid axis in depressive patients and healthy subjects in relation to the hypothalamic–pituitary– adrenal axis. Psychiatry Research, 47, 7 –21.
4. World Medical Association General Assembly. (2004) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Journal of International Bioethique, 15, 124– 129.
5. Berger, A., Drosten, C.H., Doerr, H.W., Sturmer, M. &Preiser, W. (2004) Severe acute respiratory syndrome (SARS) – paradigm of an emerging viral infection. Journal of Clinical Virology, 29, 13–22.
6. Sellmeyer, D.E. & Grunfeld, C. (1996) Endocrine and metabolic disturbances in human immunodeficiency virus infection and the acquired immune deficiency syndrome. Endocrine Reviews, 17, 518 – 532.

7. Hautala, T., Sironen, T., Vapalahti, O., Paakko, E., Sarkioja, T., Salmela, P.I., Vaheri, A., Plyusnin, A. &Kauma, H. (2002) Hypophy- seal hemorrhage and panhypopituitarism during Puumala Virus Infection: Magnetic Resonance Imaging and detection of viral anti- gen in the hypophysis. Clinical Infectious Diseases, 35, 96 –101.
8. Parmar, R.C., Bavdekar, S.B., Sahu, D.R., Warke, S. &Kamat, J.R. (2001) Thyroiditis as a presenting feature of mumps. PediatricInfec- tious Disease Journal, 20, 637 – 638.
9. Tso, E.Y., Tsang, O.T., Choi, K.W., Wong, T.Y., So, M.K., Leung, W.S.,Lai, J.Y., Ng, T.K. & Lai, T.S., Princess Margaret Hospital SARS Study Group. (2004) Persistence of physical symptoms in and abnormal laboratory findings for survivors of severe acute respiratory syndrome. Clinical Infectious Diseases, 38, 1338.
10. Chan, K.S., Zheng, J.P., Mok, Y.W., Li, Y.M., Liu, Y.N., Chu, C.M. & Ip, M.S. (2003) SARS: prognosis, outcome and sequelae. Respirology, 8, S36 – S40.
11. Tafet, G.E. &Bernardini, R. (2003) Psychoneuroendocrinological links between chronic stress and depression. Progress in Neuropsy- chopharmacology and Biological Psychiatry, 27, 893 – 903.
12. Ehlert, U., Gaab, J. & Heinrichs, M. (2001) Psychoneuroendocrino- logical contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamic-pituitary-adrenal axis. Biological Psychology, 57, 141–152.
13. Abelson, J.L. & Curtis, G.C. (1996) Hypothalamic–pituitary–adrenal axis activity in panic disorder. 24-hour secretion of corticotropin and cortisol. Archives of General Psychiatry, 53, 323 – 331.
14. Demitrack, M.A. &Crofford, L.J. (1988) Evidence for and patho- physiologic implications of hypothalamic–pituitary–adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Annals of the New York Academy of Sciences, 840, 684 – 697.
15. Yehuda, R. (2003) Hypothalamic–pituitary–adrenal alterations in PTSD: are they relevant to understanding cortisol alterations in cancer? Brain, Behavior, and Immunity, 17 (Suppl. 1), S73 – S83.
16. Oelkers, W. (1996) Dose-response aspects in the clinical assessment of the hypothalamic–pituitary–adrenal axis, and the low-dose adren- ocorticotropin test. European Journal of Endocrinology, 135, 27 – 33.
17. Rasmuson, S., Olsson, T. & Hagg, E. (1996) A low dose ACTH test to assess the function of the hypothalamic–pituitary–adrenal axis. Clinical Endocrinology, 44, 151 – 156.
18. Dickstein, G., Spigel, D., Arad, E. &Shechner, C. (1997) One micro- gram is the lowest ACTH dose to cause a maximal cortisol response. There is no diurnal variation of cortisol response to submaximal ACTH stimulation. European Journal of Endocrinology, 137, 172 – 175.
19. Abdu, T.A.M., Elhadd, T.A., Neary, R. & Clayton, R.N. (1999) Com- parison of the low dose short Synacthen test (1 g), the conventional dose short Synacthen test (250 mg), and the insulin tolerance test for the assessment of the hypothalamic–pituitary–adrenal axis in patients with pituitary disease. Journal of Clinical Endocrinology and Metabolism, 84, 838 – 843.