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Early Attention Impairment in a Patient with COVID-19

Running head: Cognitive dysfunction in COVID-19

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ABSTRACT:

A 47-year-old physician suddenly noticed a persistent difficulty maintaining attention. He was awake, alert, and oriented. After two hours he developed fever, ageusia, and anosmia. He denied any previous history of psychiatric illness and was hydrated at the time of the subjective attention impairment. On admission, the patient remained oriented. He reported the persistence of attention problems, anosmia, and mild fatigue. The oxygen saturation 99% while he was breathing ambient air. Laboratory tests were unremarkable. A high-resolution computed tomography of the chest was normal. Nasopharyngeal and throat swabs specimens on reverse transcription-polymerase chain reaction analysis tested positive for SARS-CoV2. On illness day 3, the examination was unchanged, but he continued to complain of difficulties to stay focused. Then, he performed an

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objective attention test. The test demonstrated a moderate attentional impairment. On day 6, the patient reported a subjective worse in his concentration and performed a second test. Although his physical examination remained normal, the attention performance was worse as compared to day 3. Eight hours after worsening of attention impairment, the patient's oxygen saturation dropped to 94%. From illness days 9 to 14, the patient evolved with clinical improvement. On day 10, a third objective attention test indicated a mild deficit. On day 16, he did not report any other symptom and the attention test was completely normal. Then, the patient returned to work. Neurological symptoms had been previously described in COVID- 19 patients. However, no previous research had investigated early cognitive deficits preceding the traditional symptoms.

Keywords: Covid-19; SARS-CoV-2; Attention; Variability of Reaction Time; Neuropsychology; Central Nervous System.

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INTRODUCTION:

The Angiotensin converting enzyme (ACE2) serves as the main entry into cells for SARS-CoV2 [1]. The ACE2 and ACE2 mRNA expression are found in the Central Nervous System (CNS) [2]. In addition, SARS-CoV2 has been detected in the neurons of infected patients, following the distribution of ACE2 in the CNS [3]. Accordingly, neurologic events have been described in COVID-19 patients [4-6]. Angiotensin II is the main active product of the renin-angiotensin system (RAS). Previous studies have implicated the brain RAS in cognitive functions [7]. Therefore, changes in the Renin-Angiotensin-System within the brain may cause cognitive symptoms. However, as far as we know, no previous research has investigated cognitive dysfunction in COVID-19 patients. A signed informed consent was obtained from the patient authorizing publication.

CASE PRESENTATION:

A 47-year-old physician suddenly noticed a persistent difficulty maintaining attention while driving home. He was awake, alert, and oriented (AAOX4), and described his symptom as an unusual trouble to stay focused. After two hours he developed fever, ageusia, and anosmia. He denied any previous history of psychiatric illness and was hydrated at the time of the subjective attention impairment. On admission, the patient remained AAOX4. However, he reported the persistence of attention problems, anosmia, ageusia, and mild fatigue. The body temperature was 36.6°C, the blood pressure 122/68 mmHg, the pulse 72 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen

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saturation 99% while he was breathing ambient air. Lung auscultation revealed no rhonchi, crackles, or wheezing. Laboratory tests were unremarkable (SA). The antigen test for influenza A and B was negative. A high-resolution computed tomography (HRCT) of the chest was normal (SA). Nasopharyngeal and throat swabs specimens on reverse transcription-polymerase chain reaction analysis tested positive for SARS-CoV2.

On illness day 3, he continued to complain of difficulties to stay focused. Then, his attention performance was objectively assessed with the aid of the Continuous Visual Attention Test (CVAT) (Fig. 1). The CVAT is a culture-free instrument, has high test-retest reliability, and evaluates not only global attention but also all the specific attention subdomains [8-10]. On this day (3rd), the CVAT performance corroborated his subjective attention complains (Fig. 2, Table 1). He exhibited a moderate attentional impairment in 2 out of the 4 attention subdomains as compared to the normative values (males, 45-50 years old).

On day 6, the patient reported a subjective worse in his concentration and performed a second CVAT. Although his physical examination remained normal, the CVAT performance was worse as compared to day 3. He was impaired in 3 out of the 4 attention subdomains (Fig. 2, Table 1). Considering the sustained-focused-attention subdomain, he performed above the 95th percentile as compared to age and-sex matched normative data (a higher percentile indicates a worse performance). Thus, his attentional performance was severely impaired. Eight hours after the worsening of his attention problem, there was a change in the respiratory status when the patient's oxygen saturation dropped to as low as 94%

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while he was breathing ambient air. The timing of illness progression is consistent with previous reports on signs of worsening of the general symptoms in the second week after illness onset (median at day 8).

From illness days 9 to 14, the patient evolved with clinical improvement. On day 10, the third CVAT indicated only a mild deficit in only one attention subdomain (Fig. 2, Table 1). On day 14, another HRCT (SA) showed discrete patchy ground-glass opacities in the inferior lobes. On day 16, he did not report any other symptom and the CVAT was completely normal (Fig. 2, Table 1) . Then, the patient returned to work.

DISCUSSION:

This report suggests that attention difficulties may appear before the traditional clinical diagnosis of COVID-19. COVID-19 may cause changes throughout the brain and body, not merely in the respiratory system. This finding can be added to a growing body of evidence that ACE2 deficiency results in impaired cognitive function [7]. A key aspect of this case was the decision made by the patient to seek medical help after the sudden attention impairment. The identification of a possible SARS–CoV-2 infection allowed for prompt isolation. An early attention complain was the first clinical manifestation. A worsening in attention performance on day 6 preceded the maximum drop in patient's oxygen saturation observed on the next day (7^{th} day). The patient was not sleep-deprived or presenting fever when he performed the CVATs. Consequently, for safety

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reasons returning to work was only allowed after the entire recovery of the attention impairment.

Disclosure Statement:

The authors have no conflict of o interest to declare.

Authors Contributions:

All authors contributed equally to the manuscript.

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Fig 1: Description of the Continuous Visual Attention test (CVAT). The CVAT begins with written instructions on the screen (A): “In this test, the computer alternately displays the indicated figures in the center of the screen. You must press the spacebar using your dominant hand as fast as you can whenever the star appears in the center of the screen. If the other figure appears, you should not press the space bar.” The target (B) remains on the screen for 250 milliseconds (ms). The non-target (C) also remains on the screen for 250 ms. Inter-stimulus time interval varies between 1, 2, and 4 seconds, equally distributed along the test. The test lasts 15 min. Variables: Omission Errors (OE), Commission Errors (CE), average Reaction Time of the correct responses (RT), and Variability of Reaction Time (VRT). Impaired performance could be explained by four conditions: (i) a drop in vigilance caused by falling activation which causes slow

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RTs (alertness subdomain); (ii) occasional lapses in attention as test progresses, affecting the stability of response times which causes an increase in the variability of the RTs (VRT) (sustained-attention subdomain); (iii) failure of focused attention, severe enough to result in OEs (focused-attention subdomain); and (iv) inability to control inadequate responses (impulsivity subdomain) resulting in a high number of CEs. The CVAT is open for registered psychologists upon request. Versions in English, Portuguese, and Spanish. Adapted from Schmidt SL, Schmidt GJ, Padilla CS, et al. Decrease in Attentional Performance After Repeated Bouts of High Intensity Exercise in Association-Football Referees and Assistant Referees. Frontiers in Psychology. 2019;10.

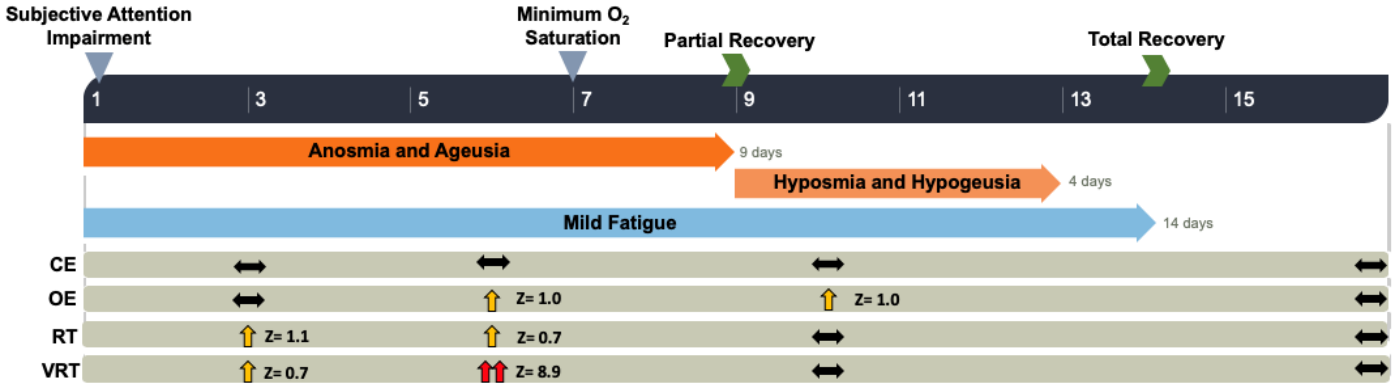

Fig. 2: Timeline showing general symptoms and impaired attention functioning.

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The CVAT was used to assess objective attention performance on days 3, 6, 10, and 16. For each variable of the CVAT, the population mean for the same age and sex of the patient (male, 45 to 50 years old) is set to zero (percentile 50%). The use of a standardized unit (Z scores) allows direct comparisons across the different variables. Performance between the 75^{th} and 25^{th} percentiles is considered normal (horizontal arrows). Moderate impairment is defined by performance between the 75^{th} and 95^{th} percentiles (vertical yellow arrows). A value higher than the 95th percentile is considered a severe impairment (double vertical red arrow). On day 1, the patient reports a subjective attention impairment. On illness day 3, the patient performs worse than the 75^{th} percentile in two subdomains (VRT and RT) indicating a moderate attention impairment. On day 6, the patient performs worse than the 75^{th} percentile in all variables of the CVAT except CE, indicating a severe impairment. VRT is the most affected variable, followed by OE. Thus, the sustained-focused subdomain is the most affected subdomain. Note that the increase in VRT seems to be independent of RT. On day 10, there is a mild deficit on only one variable (OE). On day 16, his performance is within the normal range. Abbreviations CE: Commission errors; OE: Omission errors; RT: Reaction Time; VRT: Variability of Reaction Time; CVAT: Continuous Visual Attention Test.

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Illness Day / **CVAT Variables**	**1**	**3**	**10**	**16**
CE (impulsivity)	0	0	0	-0.5
OE (focused-attention)	0	1.0	1.0	-1.0
RT (alertness)	1.1	0.7	0.4	-0.8
VRT (sustained-attention)	0.7	8.9	-0.8	-1.45
Global Assessment	Moderate Impairment	Severe Impairment	Mild Impairment	Normal

Table 1: Z-Scores (Variables of the Continuous Visual Attention Test) For each variable of the CVAT, the population mean for the same age and sex of the patient group is set to zero. The use of a standardized unit allows direct comparisons across the different variables. Positive values indicate worse patient´s performance as compared to the normative values (males, 45 to 50 years old). For each CVAT variable, a performance between the 25th and 75th percentiles is considered within the normal range (green). A value higher than the 75th percentile is considered a clinically relevant impairment

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(orange). During the disease, all attention subdomains are affected except the *impulsivity* subdomain. The failure in the *sustained-focused* subdomain is indicated by a markedly increase in the VRT, specially on day 6. The results cannot be explained by fatigue because the prominently increase in the VRT variable is independent of the RT variable. Abbreviations CE: Commission errors; OE: Omission errors; RT: Reaction Time; VRT: Variability of Reaction Time; CVAT: Continuous Visual Attention Test.