LETTER TO THE EDITOR

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Stress in Brazilian patients with Inborn Errors of Immunity during the SARS-CoV-2 pandemic

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Key words

COVID-19; SARS-CoV-2; inborn errors of immunity; pandemic; stress.

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To the Editor,

the COVID-19 pandemic severely impacted vulnerable IEI patients (1). To assess the impact is this specific population, an online stress questionnaire was administered to individuals with IEI at two time points during the pandemic: May-June 2020 and May-June 2021. All patients with IEI met the diagnostic criteria of the European Society for Immunodeficiencies, received ongoing care at a specialized immunology center, and were aged 12-80 years. A control group (CG) participated by completing the PSS-4 during the second assessment period (May-June 2021). The CG consisted of healthy individuals aged 18-45 years. Informed consent was obtained from all study participants.

Stress levels were assessed using the abbreviated four-item version of the Perceived Stress Scale (PSS-4; Portuguese version) (2). The maximum score is 16; higher scores indicate higher stress levels. One hundred and one IEI patients completed both questionnaires. The mean age was 30.5 years, 64% being women. Predominantly antibody defects were present in 80 patients (80.8%). Most participants were adolescents (39.6%), and adults aged 20 to 44 years (33.7%). **Table I** displays the clinical diagnoses and general characteristics of the IEI patients and their perceptions of the COVID-19 pandemic at the initial assessment period.

The mean IEI PSS-4 score was high during both assessments (8.85 ± 2.23 at the first assessment and 8.93 ± 2.14 at the second), showing no significant difference between them. No difference between them. No significant differences related to sex and age were observed, however adolescents showed non-significantly higher PSS-4 means. Additional findings are presented, and the mean PSS-4 score for each IEI group are presented in **table II**.

One hundred and one healthy individuals completed the PSS-4 in 2021, with a mean age of 24.3 years, and the majority were women (64%). The CG reported a mean PSS-4 score of 7.30 ± 1.23. The CG reported a mean PSS-4 score of 7.30±1.23, values significantly lower than the EII group (p = 0.00). Comparisons between the mean PSS-4 CG and each EIE group are shown in **table II**.

Data on COVID-19 in patients with IEI started to surface by the end of 2020. Goudouris *et al.* reported a mortality rate in patients with IEI reaching 5% (3): twice as high as the average mortality rate observed in the Brazilian population (4). Never-

Table I *- General features of the patients with IEI studied and their perceptions about the Coronavirus pandemic at the beginning time.*

Knowledge about the existence of the Coronavirus	100.0%
Clinical diagnosis	
CVID	46.4%
Agammaglobulinemia	4.0%
Other humoral deficiencies*	30.3%
Combined immunodeficiency	12.1%
Immune dysregulation	9.0%
IVIG monthly	94.0%
Antibiotic prophylaxis	40.6%
Maintain regular treatment	37.6%
Had been hospitalized in a ward >3 times	53.5%
Had been in an ICU at least once in their lifetime	33.6%
Recognize the symptoms of SARS-CoV-2 infection	71.3%
Recognized protective measures	93.1%
Washing your hands with soap and water works just like using 70% alcohol gel	88.1%
Fear of getting sick	90.1%
Fear of a family member becoming ill	98.0%
Do you know someone who fell ill with COVID	64.4%
Became more scared after learning that an acquaintance had become ill	51.5%
Patients with IEI are at higher risk of becoming infected	96.0%
Believe you can become infected without regular treatment	92.1%
Anxiety	
Normal, how I always felt before	13.9%
Anxious/distressed, but not afraid	32.7%
Anxious/distressed and afraid	41.6%
Very afraid	11.9%
Fear to die	
Never had	17.8%
I was afraid before, but without compromising my QoL	20.8%
I was afraid before, to the detriment of QoL	11.9%
I started to be afraid due to the coronavirus	30.7%
Always had	18.0%

First questionnaire assessment; n = 101. IVIG: Intravenous Human Immunoglobulin; ICU: Intensive Care Unit; CVID: common variable immunodeficiency. *Polysaccharide antibody deficiency (SAD), hypogammaglobulinemia, IgA deficiency and IgG subclass deficiency.

theless, no data were found that evaluated stress perception in this patient cohort using the PSS-4.

Pandemic-era studies using the PSS-4 revealed diverse stress levels across populations. Zhao *et al*. reported a mean PSS-4 score of 8.39 ± 2.33 in physicians presenting with symptoms consistent with irritable bowel syndrome (5). Steel *et al*. identified cancer patients with significantly elevated PSS-4 scores compared to normative data (6). Pham *et al.* suggested that stress adversely affected patients with rheumatoid arthritis (7). In contrast, stud-

Table II *- Perceived Stress Scale (PSS-4) items in the two assessments in patients with inborn errors of immunity and the PSS-4 average by diagnosis and comparison with control group (n = 101).*

	1a. Assessment (%)	**2a. Assessment (%)**	**P-value**
In the last month, how often have you felt that you were unable to control the important things in your life?			**0.030**
Never	4.0%	5.9%	
Almost never	20.8%	6.9%	
Sometimes	24.8%	38.6%	
Fairly often	22.8%	12.9%	
Very often	27.7%	35.6%	
In the last month, how often have you felt confident about your ability to handle your personal problems?			0.418
Never	5.9%	14.9%	
Almost never	15.8%	8.9%	
Sometimes	23.8%	22.8%	
Fairly often	19.8%	14.9%	
Very often	34.7%	38.6%	
In the last month, how often have you felt that things were going your way?			0.653
Never	6.9%	5.9%	
Almost never	3.6%	29.7%	
Sometimes	24.8%	31.7%	
Fairly often	24.8%	20.8%	
Very often	6.9%	11.9%	
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?			0.405
Never	3.0%	6.9%	
Almost never	11.9%	6.9%	
Sometimes	21.8%	24.8%	
Fairly often	24.8%	17.8%	
Very often	38.6%	43.6%	

→

n (%)	PSS-4		
	1a. Assessment#	2a. Assessment#	P-value
PSS-4 score			
Total IEI; 101 (100)	8.85 ± 2.23	8.93 ± 2.14	0.769
PSS-4 by diagnosis			
CVID; 46 (46.4)	8.87 ± 2.28	8.80 ± 2.26	0.891
Humoral deficiencies$^{\gamma}$; 34 (33.6)	8.73 ± 1.83	9.18 ± 2.02	0.421
Combined immunodeficiencies; 2 (12.1)	10.18 ± 2.04	9.00 ± 2.04	0.253
Comparison of controls and IEI at 2a. Assessment	**Controls# (n = 101)**	**IEI# (n = 101)**	
Mean PSS-4 score	7.30 ± 1.23	8.93 ± 2.14	**0.000**
Comparison of controls to each specific IEI group			
CVID (n = 46)		8.80 ± 2.26	**0.009**
Humoral deficiencies$^{\gamma}$ (n = 34)		9.18 ± 2.02	**0.001**
Combined immunodeficiencies (n = 12)		9.00 ± 2.04	**0.015**
Immune dysregulation (n = 9)		8.00 ± 2.00	0.328

Descriptive level of the McNemar test was used for P-values; γ: polysaccharide antibody deficiency (SAD), hypogammaglobulinemia, agammaglobulinemia, IgA deficiency and IgG subclass deficiency; IEI: Inborn errors of immunity; CVID: common variable immunodeficiency. #Mean (± SD).

ies of individuals without reported comorbidities revealed mean PSS-4 scores of 6.31 in Australians (8) and 7.00 in young Americans (9).

Our data clearly show that EII patients had higher levels of stress than controls. Interestingly, when individual IEI subgroups were compared to the CG, statistically significant differences were observed in all but the immune dysregulation subgroup (**table II**). Despite extensive efforts to mitigate the COVID-19 pandemic, our findings demonstrate elevated stress levels among individuals with IEI during that period. This study highlights the critical need to identify patients experiencing heightened perceived stress during crises. Future research is warranted to elucidate this association and optimize management strategies to enhance overall patient care.

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Contributions

All authors: conceptualization, formal analysis, methodology, writing – review & editing. LSS, DS, GWF: data curation. LSS, CSA, DS, GWF: funding acquisition. LSS: investigation, writing – original draft. LSS, CSA: project administration, validation, visualization. LSS, CSA, LNT, DS, RRLG, GWF: supervision. RRLG, GWF: validation. DS: project administration. GFW, DS, LSS, CSA: resources.

Conflict of interests

The authors declare that they have no conflict of interests.

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