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ORIGINAL ARTICLE

Impacts of the COVID-19 Pandemic on the Mental Health and Motor Deficits in Cuban Patients with Cerebellar Ataxias

Yasmany González-Garcés[1] · Yennis Domínguez-Barrios[2] · Arianna Zayas-Hernández[3] · Aldo A. Sigler-Villanueva[4] · Nalia Canales-Ochoa[1] · María O. Hernández Oliver[5] · María B. Ramírez-Bautista[6] · Alberto Caballero-Laguna[7] · Eduardo Arrufat-Pie[8] · Frank J. Carrillo-Rodes[1] · Jacqueline Medrano-Montero[1] · Yanela Rodríguez-Álvarez[9] · Osiel Gámez-Rodríguez[10] · Leonardo A. Guerra-Rondón[11] · Osvaldo Aguilera-Batista[12] · Yaimee Vazquez-Mojena[13] · Roberto Rodríguez-Labrada[13] · Luis Velázquez-Pérez[14] · on behalf of the Cuban Hereditary Ataxias Network

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Abstract
Although there are no convincing evidences of detrimental effect of SARS-CoV2 infection on the cerebellum, the COVID-19 pandemic could impact the life quality of patients with cerebellar ataxias, but few studies have addressed this concern. To assess the motor and mental health changes caused by the COVID-19 pandemics in Cuban patients with cerebellar ataxias, three hundred four patients with cerebellar ataxias and 167 healthy controls were interviewed for risks of exposure to COVID-19, and the self-perception of the pandemics' impact on the disease progression and on the mental health. All subjects underwent the Hospital Anxiety and Depression Scale. The patients reported low exposition to SARS-CoV2 infection, but one case was confirmed with a mild COVID-19. Overall, depressive and anxiety symptoms were significantly and marginally increased in patients, respectively, with higher scores in cases with severe and moderate ataxia. Positive patient's impression of psychopathological changes was associated to increased age, age at onset, and anxiety. Sixty-seven patients had a positive self-perception of ataxia progression, which was mainly influenced by higher anxiety scores but not by the adherence to at-home exercise programs. However, the practice of physical exercise was related with lower depression and anxiety scores, but this therapeutical effect was not significantly influenced by the disease stage. We demonstrated the negative effect of the COVID-19 pandemic on the mental and motor deficits in Cuban patients with cerebellar ataxias and the positive effect of the at-home physical exercise programs on their mental well-being. These findings give rationales to develop tele-medicine approaches to minimize these health impacts and to study the long-term effects of such sequelae and accordingly define their treatments.

Keywords Cerebellar ataxias · Mental health · COVID-19 · SARS-CoV2 · Pandemic

Introduction

Humanity is suffering from one of the most severe pandemic in world history: the COVID-19 (Coronavirus Disease 2019). Almost all nations have transmission, and the number of infected people already exceeds 95 million, with more than two millions of deaths by January 17, 2021 [1]. COVID-19 is caused by a new coronavirus called SARS-CoV2. Its main clinical manifestations include fever, fatigue, dry cough, myalgia, anosmia, and dyspnea and in some cases, but a high frequency of asymptomatic subjects is reported, which complicates the management of the pandemic [2, 3].

The disease represents additional challenges for the medical care of patients with chronic diseases, such as diabetes mellitus, obesity, and respiratory diseases, and neurodegenerative diseases due to the SARS-Cov2 infection can increase the severity and progression of these symptoms [4]. The reasons why patients with neurodegenerative diseases need a special attention during the COVID-19 pandemics are supported by

Yasmany González-Garcés and Yennis Domínguez-Barrios both authors had the same contribution

✉ Roberto Rodríguez-Labrada
roberto.rodriguez@cneuro.edu.cu

✉ Luis Velázquez-Pérez
velazq63@gmail.com

Extended author information available on the last page of the article

the known neurotropism of the SARS-CoV2 [5]. In fact, there are several reports of nervous system involvement in COVID-19 [6]. Moreover, it is known that patients with neurological diseases are more susceptible to the effects of severe respiratory infections, mainly in those with brainstem (mainly the bulb) involvement, where the vital centers of circulation and respiration are located [7]. Within this specific group of diseases, the cerebellar ataxias are well represented due to the known involvement of brainstem and the high connection of this structure with the cerebellum [8]. The cerebellar ataxias are a clinically heterogeneous group of neurological diseases caused by acute or chronic (degenerative) involvement of the cerebellum and its afferent and efferent connections, spinal cord, peripheral nerves, and the brainstem.

Most of cerebellar ataxias have a genetic etiology, denoted by a large group of autosomal dominant cerebellar ataxias (also called spinocerebellar ataxias) and the autosomal recessive cerebellar ataxias (e.g., Friedreich's ataxia, ataxia telangiectasia). Other cerebellar ataxias are secondary to a primary etiology, such as traumas, infections, drugs, and alcoholism, whereas other ones are classified as sporadic ataxias [9].

Available data during the COVID-19 outbreak suggest that cerebellum function seems not to be so compromised by the SARS-CoV2 infection. Ataxia was reported in only 1% of a large cohort of hospitalized COVID-19 patients in China [10]. In addition, other single cases with cerebellar ataxia have been reported in distinct populations [11–15]. The scarce cerebellar symptomatology of COVID-19 patients is supported by previous experimental studies conducted in transgenic mice for the angiotesin-converting enzyme receptor 2 in which the nasal introduction of a SARS-CoV1 virus strain did not caused the viral dissemination to the cerebellum [16]. In spite of this apparent low vulnerability of cerebellum to the SARS-CoV2 infection, the multisystemic nature of the many cerebellar ataxias could confer an additional susceptibility to the novel coronavirus in these patients and consequently promote worsening of the clinical cerebellar and/or non-cerebellar symptoms.

Unfortunately, there are few data about the impact of the SARS-CoV 2 infection and/or the COVID-19-enforced social isolation on the motor and psychopathological features of the cerebellar ataxias. The first study included 307 Chinese patients with spinocerebellar ataxias (SCA) and identified increased anxiety in 35% of the cases and depression in 57% [17]. Recently, a survey in 20 Italian patients with Friedreich ataxia reported the self-perception of worsening in global health in 60% of cases as result of the physiotherapy interruption [18].

Thus, as Cuba has a large number of cerebellar patients, with the highest prevalence rate of SCA2 at worldwide [19], and this country has not escaped from the COVID-19 (18.151 cases and 170 deaths, by January 17, 2020; country population: 11,193,470 inhabitants) [1], the Cuban population of cerebellar patients is attractive to evaluate the motor and mental health changes caused by the COVID-19 pandemics in the cerebellar ataxias.

Patients and Methods

Subjects

Three hundred four (170 females/134 males) Cuban patients with cerebellar ataxias from 13 Cuban provinces were recruited to participate in this study between July 15 and September 15, 2020. Mean age (± SD; range) of this group was 51.4 (± 14.9; 19–90) years old, whereas age at onset was 38.2 (± 13.2; 7–70). Mean disease duration of patients with cerebellar ataxias was 14.3 (± 9.9; 1–59). Mean SARA score was 11.54 (± 7.4; 0–35), whereas INAS count was 3.40 (± 1.4; 0–7).

Two hundred sixty-one patients had SCA2, 6 SCA3, 2 SCA7, and 2 SCA8, whereas in 20 cases, the subtype of SCA was unknown. In addition, 2 cases had Friedreich ataxia, and one has ataxia telangiectasia. Seven subjects were diagnosed with sporadic ataxia, and three cases showed an acquired ataxia. Regarding the disease stage, 31 cases were in prodromal stage of SCA2, whereas 155 patients exhibited a slight ataxia, followed by 81 patients with moderate ataxia and 37 with severe ataxia.

Further, a group of 167 individuals without personal and familiar history of ataxia were used as controls. The mean age of this group was 45.6 (± 15.8; 22–80). All procedures were in accordance with the declaration of Helsinki and the standards of the institutional ethics committee. All participants gave their written informed consent prior to the experiments.

Methods

All subjects underwent a standardized questionnaire including general demographic information, risks of exposure to COVID-19, and the self-perception of the pandemics impact on the disease progression and on the mental health as well as the adherence to at-home neurorehabilitation. The risk of exposure to COVID-19 was assessed considering the presence of suspicious symptoms of COVID-19; the contact with confirmed patients with the SARS-CoV2 infection; and the presence of COVID-19 confirmed patients in their neighborhood. The self-perception of motor impact of the pandemics was evaluated throughout the patient's global impression of ataxia progression within this period. The mental health was assessed by the Hospital Anxiety and Depression Scale (HADS) [20]. Clinical measures included the Scale for Assessment and Rating of Ataxia (SARA) [21] and the

Inventory of Non-ataxia Symptoms (INAS) [22] scores obtained within the last 12 months before the pandemic.

Statistical Analysis

Normality of variables was evaluated using the Kolmogorov–Smirnov tests. For descriptive statistics of continuous variables, the means and standard deviations were calculated, whereas categorical variables were expressed as proportions. Mean comparisons were assessed by the Student's *t* tests (two-tailed) followed by Bonferroni correction for multiple comparisons. The effects of the disease stage and the at-home neurorehabilitation on the HADS scores were assessed using ANOVAs followed by Tukey HSD post-hoc tests. All analyses were performed using the IBM SPSS STATISTICS V23.000.

Results

Fifteen patients had risks of exposure to COVID-19 (4.9%), among them 10 reported suspicious symptoms of the disease, three were contacts of RT-PCR confirmed patients with COVID-19, and four had neighbors that were confirmed with COVID-19. In the case of the control group, no case was confirmed with the SARS-CoV2. However, 15 cases exhibited suspicious symptoms, 14 were contact of COVID-19 patients, and six had neighbors that were confirmed with COVID-19. Findings of the frequency analyses are shown in Table 1.

In our cohort, one out of 304 (0.33%) patients with cerebellar ataxias was diagnosed with COVID-19. This is the case of a 19-year-old female with clinical and molecular diagnosis of SCA2, who lives in Havana. She was admitted to the respiratory unit of the "Luis Diaz Soto" Hospital (Havana, Cuba) due to fever symptoms, accompanied by cough. RT-PCR test was positive for the throat swab sample. The patient was treated following the Cuban protocol for the treatment of COVID-19 until her hospital discharge (16 days after admission), but the symptoms disappeared 3 days after hospitalization. After her discharge, the patient referred no worsening of ataxia symptoms, nor psychopathological sequelae as consequence of the SARS-CoV2 infection.

Regarding the mental health, the analysis of the HADS score reveals a significant increase of mean score for depression in patients when compared with controls, whereas for anxiety, there are no significant differences (Fig. 1a). Frequency analysis discloses a significantly higher proportion of subjects with abnormal HADS scores for depression in the patient's group (Fig. 1b). In the case of the HADS score of anxiety, the frequency analysis reveals no intergroup differences (Fig. 1c). The one-way ANOVAs revealed a significant effect of the disease stage on the HADS scores. The depression score of patients with severe ataxia was significantly higher than in the other disease stages, while moderate cases also differed from slight and prodromal cases. However, there is no difference between these latter two groups (Fig. 1d). For the anxiety scores, the differences were only observed between the severe cases and the slight and prodromal cases, respectively. Although the subjects in prodromal stage showed higher values of anxiety score than slight cases, the difference is not statistically significant (Fig. 1e).

On regards the patient's impression of psychopathological impacts of the pandemic, 78 patients (25.7%) referred psychological alterations as result of the confinement. *T* test analyses disclosed that these patients had an increased age (55.1 ± 16.3 vs 50.1 ± 14.2; $p = 0.010$), age at onset (41.9 ± 13.9 vs 37.1 ± 12.8; $p = 0.014$),) and anxiety HADS score (6.2 ± 5.0 vs 3.6 ± 3.7; $p < 0.0001$) when compared with patients referring no such changes. No intergroup differences were observed for the disease duration, HADS depression score, SARA score, and INAS count (data not shown).

Analysis of the patient's global impression of disease progression during the pandemic revealed a worsening of ataxia in 67 patients (22.0%). These cases had a mean anxiety HADS score significantly higher than patients that did not disclose ataxia worsening (5.41 ± 5.57 vs 3.95 ± 3.75; $p = 0.013$). However, neither age, age at onset, disease duration, depression HADS score, SARA score, nor INAS scores were statistically different.

Regarding the effect of the physical exercises during the confinement, 113 cerebellar ataxia patients (37%) were adhered to at-home neurorehabilitation procedures. *T* test analyses showed lower depression (3.50 ± 3.39 vs 4.80 ± 4.86; $p = 0.013$) and anxiety (3.63 ± 3.96 vs

Table 1 Risks of exposure to COVID-19 in patients and controls

Risks of exposure to COVID-19	Patients	Controls	
RT-PCR confirmed COVID-19	1 (0.3%)	0 (0%)	ns
Suspicious symptoms of COVID-19	10 (3.3%)	15 (8.9%)	$p = 0.015$
Contact with RT-PCR confirmed COVID-19 patient	3 (0.9%)	14 (8.4%)	$p < 0.0001$
Neighbors with RT-PCR confirmed COVID-19	4 (1.3%)	6 (3.6%)	ns

RT-PCR real-time polymerase chain reaction. *ns* no significant

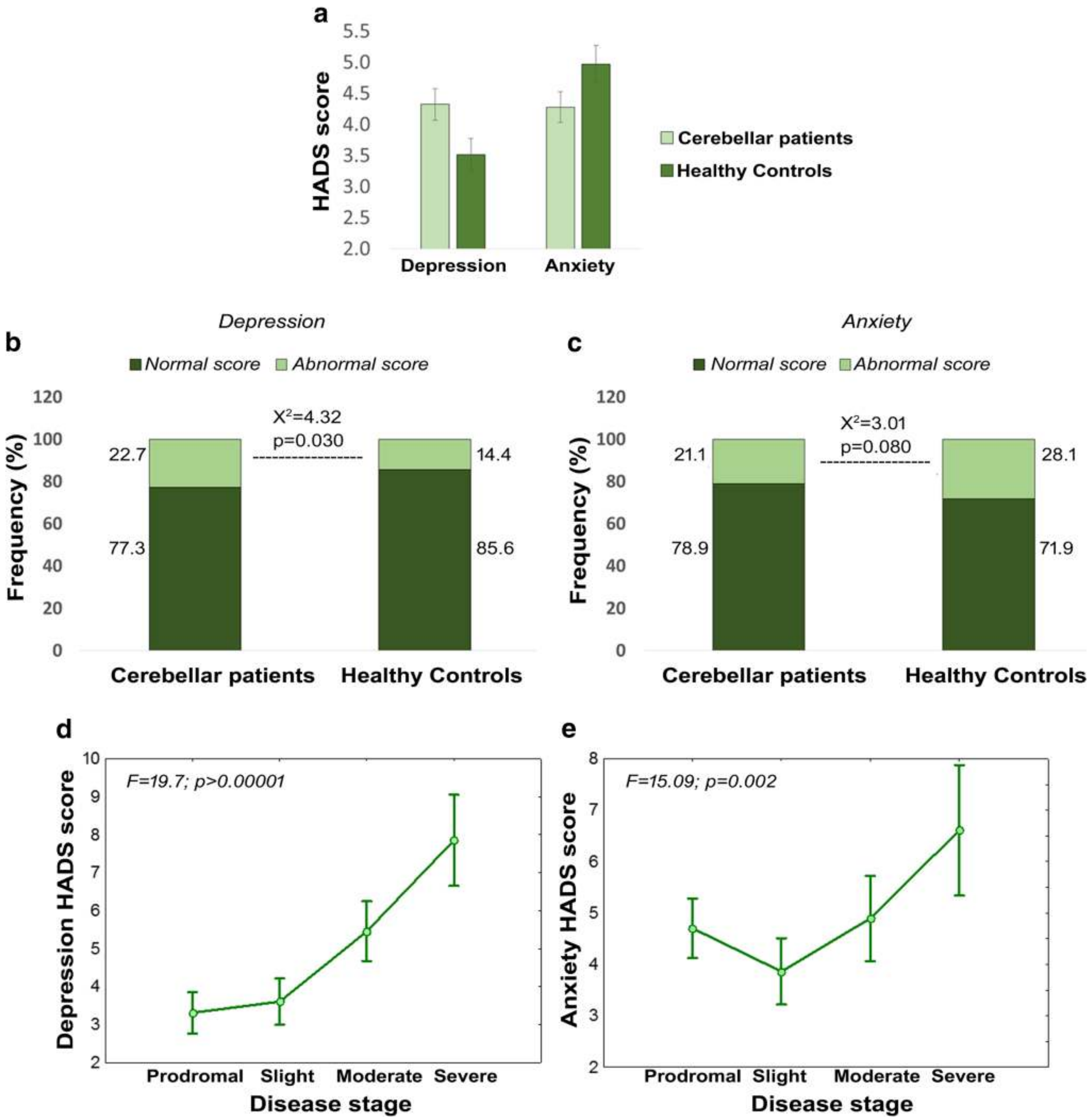

Fig. 1 Mental health impacts of COVID-19 pandemics on patients with cerebellar ataxias. **a** Mean comparisons of depression and anxiety HADS scores between patients and healthy controls. **b** Frequency analysis for abnormal depression HADS scores. **c** Frequency analysis for abnormal anxiety HADS scores. *Bars represents the standard errors. HADS: Hospital Anxiety and Depression Scale*

4.66 ± 4.38; $p = 0.041$) HADS scores in patients that performed physical exercises in comparison with those that did not. Nevertheless, the factorial ANOVAs did not revealed significant differences between both groups for none disease stage, but a marginal decrease of the depression HADS score is observed in patients with moderate and severe ataxia that underwent at-home neurorehabilitation (Fig. 2). Surprisingly, the percentage of cases that underwent at-home physical exercises was similar in the subgroups of patients that referred ataxia worsening and those declaring no worsening (38.8% vs 36.7%; $X^2 = 0.03$; $p = 0.865$).

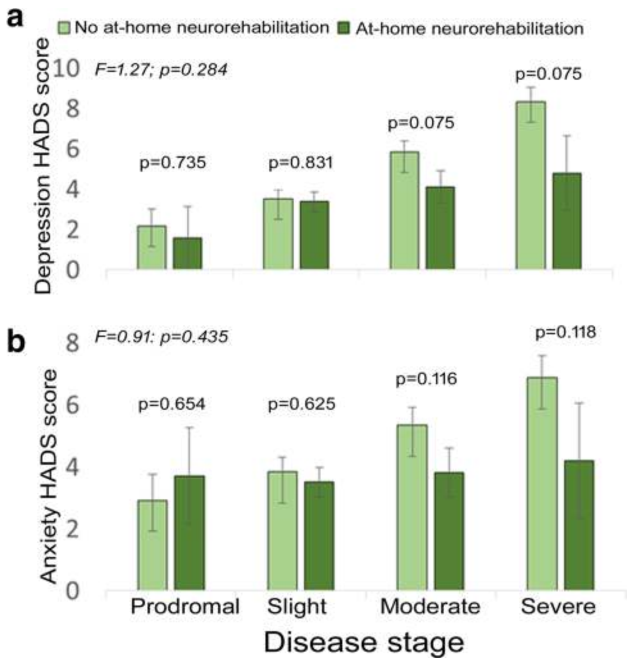

Fig. 2 Effects of the adherence to at-home neurorehabilitation and the disease stage on the depression (**a**) and anxiety (**b**) HADS scores. *Bars represents the standard errors. HADS: Hospital Anxiety and Depression Scale*

Discussion

The present paper assessed the mental and motor repercussion of COVID-19 pandemic in a large population of Cuban patients with cerebellar ataxia. The main findings were the increase of depressive symptoms and self-perceived motor deficits in spite of the reduced risk to SARS-CoV2 infection.

As expected, the exposure level to the coronavirus infection was higher in controls than patients due to the latter ones were usually more protected by self of their family restricting their movements out the home, limiting receiving visitors or even moving to other regions with lower COVID-19 incidences. Despite this lower risk, one SCA2 patient was diagnosed with COVID-19 but experienced a mild picture without discernible sequelae. Clearly, this isolated case is insufficient to search putative association between the SARS-CoV2 infection and physiopathology of SCA2 and other cerebellar ataxias which claims for further studies.

Assessing the impact of the COVID-19′s pandemic on the mental health has been priority for the understanding and management of the disease and its sequelae [23, 24]. In this study, we observed a significant increase of depressive symptoms in cerebellar ataxia patients using the HADS score. As depression is a common feature of cerebellar ataxias [25, 26], this could had been influence on the patients HADS score. Nevertheless, we believe this effect is minimized due to the application of this scale took the beginning of the COVID-19 pandemics as reference. Hence, this implies that the pandemics increased the depressive symptoms in those patients with already exhibited this picture before the pandemics or even generated it in those cases without prior depressive symptomatology.

Regarding anxiety, patients with cerebellar ataxias exhibited no significant, but marginal, increase of HADS score when compared with controls. Usually, cerebellar patients show less anxiety than depressive symptoms [26, 27], which suggest a fewer worsening of this feature as result of the COVID-19 pandemics. Additionally, systematic reviews studying the effects of viral respiratory epidemics (including COVID-19) on mental health revealed that anxiety is more common than depression in the general population [28, 29]. Therefore, the relative lower prevalence of anxiety in cerebellar patients in combination with its higher prevalence in the general population (controls) during the COVID-19 pandemics may explain these findings.

Interestingly, the HADS scores were significantly influenced by the disease stage, reflecting a worse impact of the pandemic on the mental health in patients with moderate and severe ataxia. Normally, the depressive status is closely related with the disease severity in cerebellar ataxias [25, 26], due to the negative emotional impact caused by an advanced motor disability. So, in times of crisis such as the COVID-19 pandemic, this psychological distress could be exacerbated because they feel more vulnerable and fear that the reduced contact with their physicians due to social distancing measures would affect the proper attention of their health complications. Therefore, the telehealth actions, especially the psychological interventions, should be prioritized for cases with advanced ataxia stage.

The assessment of mental health in the Chinese cohort of spinocerebellar ataxia revealed a similar pattern of more depressive than anxiety symptoms, but the proportion of such features was higher than in our cohort. This study was conducted in a period when the incidence of COVID-19 was notably elevated in China, which settled higher stressful conditions for ataxia patients than in Cuba [17]. In addition, Cuban patients have undergone a psychological rehabilitation program by various years which have increased their preparedness for these situations [30].

Agreeing with the findings of the HADS, one-quarter of the cerebellar ataxia patients disclosed psychopathological impacts as result of the confinement, which was associated with the larger age and age at onset, as well as with increased anxiety HADS score which could result from the relationship between aging and positive psychopathological perception [31].

Similar to psychopathology, various cases reported a worsening of motor deficits during the pandemic. This was associated with a higher proportion of cases referring psychopathological impacts and increased HADS scores for anxiety. Nevertheless, the adhesion to at-home physical exercise procedures did not influence on this patient's impression. Then, up to our data reflect, we suggest that the self-impression on the disease severity changes resulting from the confinement is largely influenced by psychopathological factors (mainly anxiety symptoms). This statement did not exclude the role of physical exercises on the motor deficits of ataxia patients [32], but likely, it is subjectively surpassed by the detrimental impact of psychopathological symptoms. Furthermore, as the at-home exercises were mainly unsupervised by neurorehabilitation experts is probable that some patients had performed incorrect techniques and had follow improper intensity and systematical schedules to promote motor improvements.

Nevertheless, our data suggested a positive effect of at-home neurorehabilitation on the mental health of cerebellar ataxia patients, by decreasing depressive and anxiety symptoms and consequently increasing their self-esteem and resilience to this stressful event. This therapeutical effect seems to be higher in cases with moderate and severe ataxia, but the differences in the number of patients in each disease stage should be considered during the interpretation of these findings.

The protective effect of at-home neurorehabilitation on the mental health in Cuban patients with cerebellar ataxias is agree with previous studies conducted in the general population [33, 34]. Unfortunately, the study conducted in 20 patients with Friedreich ataxia did not assess the mental health of cases that adopted at-home technology-based strategies of rehabilitation [18]. Thus, these findings alongside our data call the need to implement easy and low-cost home-based physical training system for cerebellar patients during lockdown times, which is in line with the general recommendations given previously for physicians and researches focused on cerebellar ataxia management [35–37].

Considering the small incidence of COVID-19 in Cuba [1] and the low exposure level to SARS-CoV2 of the Cuban patients with cerebellar ataxia, the mental health changes described in this work could be interpreted as consequences of a nocebo effect. This is a very common phenomenon in the clinical practice consisting of adverse events induced by patient's negative expectancies about a treatment outcome [38] or by situational-contextual factors such as the COVID-19 pandemic [39]. Although the link between nocebo effect and COVID-19 is not clear, it is suggested that the large exposure to negative and alarming media's news about the pandemic and the social distancing measures can promote or exacerbate this effect [39]. Although it is expected that cerebellar ataxia patients are more likely to develop the nocebo effect due to their pre-existing mood disorders [26, 27, 40], a previous meta-analysis of placebo-controlled clinical trials revealed that this phenomenon has lower incidence in cerebellar ataxia when compared with other neurological diseases [41].

As a conclusion, this paper demonstrated the negative effect of the lockdown caused COVID-19 pandemic on the mental and motor deficits in Cuban patients with cerebellar ataxias in spite the relatively lower risk to SARS-CoV2 infection of this population. Also, we provided evidence supporting the palliative role of at-home physical exercises on these mental health consequences, setting strong rationales to implement telehealth approaches to minimize them during the confinements as well as to design follow-up assessments to determine the duration and severity of such sequelae along time and to define their treatment.

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Declarations

Conflict of Interest All authors declare no competing interests.

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Authors and Affiliations

Yasmany González-Garcés[1] · Yennis Domínguez-Barrios[2] · Arianna Zayas-Hernández[3] · Aldo A. Sigler-Villanueva[4] · Nalia Canales-Ochoa[1] · María O. Hernández Oliver[5] · María B. Ramírez-Bautista[6] · Alberto Caballero-Laguna[7] · Eduardo Arrufat-Pie[8] · Frank J. Carrillo-Rodes[1] · Jacqueline Medrano-Montero[1] · Yanela Rodríguez-Álvarez[9] · Osiel Gámez-Rodríguez[10] · Leonardo A. Guerra-Rondón[11] · Osvaldo Aguilera-Batista[12] · Yaimee Vazquez-Mojena[13] · Roberto Rodríguez-Labrada[13] · Luis Velázquez-Pérez[14] · on behalf of the Cuban Hereditary Ataxias Network

[1] Centre for the Research and Rehabilitation of Hereditary Ataxias, Libertad 26, Holguín, Cuba

[2] National Institute of Neurology and Neurosurgery "Rafael Estrada", 29th Street 139, Vedado, Plaza de la Revolución, Havana, Cuba

[3] Polyclinic "Manuel Fajardo Rivero", Urbano Noris, Holguín, Cuba

[4] University Hospital "Antonio Luaces", "Máximo Gomez" 257, Ciego de Avila, Cuba

[5] Pediatric Hospital "José Luis Miranda", "26 de Julio" Ave, Escambray, Santa Clara, Cuba

[6] University Hospital "Lucía Iñíguez", "Celia Sánchez" Avenue 1, Holguín, Cuba

[7] Clinical & Surgical Hospital "Guillermo Domínguez" Puerto Padre, Las Tunas, Cuba

[8] Clinical & Surgical Hospital "Manuel Piti Fajardo", Plaza de la Revolución, Cuba

[9] University of Camagüey, Camagüey, Cuba

[10] University Hospital "Juan Bruno Zayas", Carretera del Caney Street. Pastorita, Santiago de Cuba, Cuba

[11] Municipal Center of Medical Genetics, 1st Street, Cauto Cristo, Granma, Cuba

[12] Medical University of Holguin, Holguin, Cuba

[13] Cuban Centre for Neuroscience, Playa. 190 St. And 25th Ave., 19818, Playa, Havana, Cuba

[14] Cuban Academy of Sciences, Cuba St. 460, between Teniente Rey St. and Compostela St. Habana Vieja, 19100, Havana, Cuba