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Report

Hansen's disease and COVID-19 co-infection in Brazil

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Abstract

Background The implications of COVID-19 co-infection in patients under treatment for Hansen's disease (HD, leprosy) remain uncertain. We aimed to describe clinical characteristics, treatments, and outcomes in patients with HD and COVID-19 in Brazil.

Methods Cross-sectional study recruiting adult HD patients with PCR-confirmed COVID-19 from five HD treatment centers in Brazil between March 1, 2020, and March 31, 2021. At the time of this study, no patient had received COVID-19 vaccine.

Results Of 1377 patients under treatment for HD, 70 (5.1%) were diagnosed with COVID-19. Of these, 41 (58.6%) had PCR-confirmed COVID-19, comprising 19 men and 22 women, aged 24–67 (median 45) years. HD was multibacillary in 39/41 patients. Eight patients ceased WHO Multi-Drug Therapy for HD, three for lack of drugs, two because of COVID-19, and three for other reasons. Of the 33 who continued treatment, 26 were on the standard regimen and seven an alternative regimen. Seventeen patients were receiving oral prednisone, including nine patients with type 1 reaction, four with type 2 reaction, three with neuritis, and one with rheumatologic disease. Twelve patients were hospitalized for COVID-19, and six patients died, of whom three had hypertension and one also had type 2 diabetes and obesity.

Conclusions COVID-19 and Hansen's disease co-infection did not appear to change the clinical picture of either disease in this cross-sectional study. The wider impact of the pandemic on persons affected by HD requires follow-up and monitoring.

Introduction

Hansen's disease is endemic to Brazil, with 30,000 new cases diagnosed each year, representing 13% of all reported new cases worldwide.[1,2] Brazil is also one of the countries most severely impacted by the COVID-19 pandemic, reporting over 600,000 deaths by October 2021.[3]

Early concerns about SARS-CoV-2 co-infection in patients being treated for Hansen's disease have not been addressed satisfactorily by the small number of published studies and case

reports.[4–8] These concerns include a possible increased risk of severe COVID-19 in HD patients receiving immunosuppressive therapies and HD reactions triggered by SARS-CoV-2 infection.[9,10] HD reactions are immunological events affecting a substantial proportion of patients with HD, with a potentially long list of triggers including co-infection.[11] COVID-19 can trigger severe inflammation which, in theory, could increase the risk of HD patients developing HD reactions because of the high levels of cytokines in the pathogenesis of both conditions.[12] Similarly, whether COVID-19 might occur more frequently or with greater severity in Hansen's disease patients has not yet been determined.

Here, we report the co-occurrence of COVID-19 in patients with HD in Brazil. Our aim was to add to the limited evidence currently available by describing the clinical characteristics of HD and COVID-19 co-infected cases, the treatments received for both diseases and HD reactions, and COVID-19 mortality as the primary outcome.

Methods

Adult patients (age 18 years and older) from five Hansen's disease treatment centers in Brazil were recruited to the study from March 1, 2020, to March 31, 2021, from one center in each of the municipalities of Belém (Pará), Brasília (Distrito Federal), Vitória (Espírito Santo), Petrolina (Pernambuco), and Palmas (Tocantins). Patients were invited to participate if they had been diagnosed with COVID-19 and gave their consent to retrieval of clinical information from their medical records and to answer questions about their illnesses. Ethical approval was obtained from the research ethics committee (Comitê de Ética em Pesquisa, CEP) of the Universidade Federal do Espírito Santo (UFES), certificate no. 40347520.5.0000.5060.

Results

Of 1377 patients under treatment for Hansen's disease, 70 (5.1%) were diagnosed with COVID-19. Of these, 41 (58.6%) were confirmed by PCR, comprising 19 (46.3%) men and 22 (53.7%) women. Ages ranged from 24 to 67 (median 45, IQR 39–55) years.

Hansen's disease was multibacillary (MB) in 39/41 (95.1%) patients and paucibacillary (PB) in 2/41 (4.9%). Madrid classifications were: borderline 29 (70.7%); lepromatous eight (21.9%); tuberculoid two (4.9%); and indeterminate one (2.4%).

Eight of the 41 participants (19.5%) stopped receiving treatment for Hansen's disease for the reasons shown in Table 1. All of these patients had been on the standard WHO-MDT regimen comprising rifampicin (600 mg once per month), dapsone (100 mg daily), and clofazimine (50 mg daily plus 300 mg once per month). Of the 33 patients who continued receiving treatment, 26 were on the standard regimen, seven on alternative regimen (3 rifampicin + dapsone + minocycline; 2 rifampicin + dapsone + ofloxacin; 1 clofazimine + ofloxacin + moxifloxacin; 1 double clofazimine dose + ofloxacin).

Table 1 Reasons for stopping WHO-MDT among patients with Hansen's disease and COVID-19

Reasons for stopping WHO-MDT	Frequency
COVID-19	2
Feeling unwell	2
Kidney insufficiency	1
Lack of MDT	3
Total	8

Thirteen patients (31.7%) experienced Hansen's disease reactions while also being infected with SARS-CoV-2, comprising 9/13 with type 1 reactions and 4/13 with erythema nodosum leprosum (type 2 reaction). Seventeen patients (41.5%) were receiving oral prednisone in daily doses ranging from 10 to 60 mg, comprising all 13 patients with HD reactions plus three patients with neuritis and one patient with rheumatologic disease. One patient with type 1 and one patient with type 2 HD reactions were also receiving thalidomide, the type 1 reaction patient because of adverse reaction to long-term oral corticosteroids.

Twenty-three patients (56.1%) had no major comorbidity. Of the 18 patients with comorbidities, 14 had hypertension (11 were taking antihypertensives), five had diabetes mellitus (four taking hypoglycemic agents), five had cardiopathies, and four were obese. Comorbidities are summarized in Table 2.

The most commonly reported COVID-19 symptoms were anosmia (85.4%), asthenia (82.9%), dysgeusia (75.6%), headache (75.6%), fever (70.7%), dyspnea (70.7%), and cough (65.9%) (Table 3).

Hospitalization was required for 12 patients (29.3%), all of whom received nasal oxygen; six patients proceeded to mechanical ventilation in an intensive care unit, all of whom died (after 2, 7, 9, 10, and 15 days post-admission to ICU). Of the six patients who died from COVID-19, all had the multibacillary form of Hansen's disease and were receiving clofazimine (one patient in a double dose of 100 mg per day). Table 4 summarizes the characteristics of the patients who died.

Table 2 Comorbidities among patients with Hansen's disease and COVID-19

Comorbidity	Frequency
Hypertension	14
Diabetes	5
Heart disease	5
Obesity	4
Kidney disease	2
Cerebrovascular accident	1
Chagas disease	1
Paroxysmal nocturnal hemoglobinuria	1
Hypothyroidism	1
Peripheral venous insufficiency	1
Prediabetes	1
Acquired immunodeficiency syndrome	1

Table 3 COVID-19 symptoms among patients with Hansen's disease and COVID-19

Symptom	Frequency (%)
Anosmia	35 (85.4%)
Asthenia	34 (82.9%)
Headache	31 (75.6%)
Dysgeusia	31 (75.6%)
Dyspnea	29 (70.7%)
Fever	29 (70.7%)
Cough	27 (65.9%)
Coryza	24 (58.5%)
Odynophagia	24 (58.5%)
Vertigo	23 (56.1%)
Nausea	21 (51.2%)
Persistent symptoms	21 (51.2%)
Diarrhea	16 (39.0%)
Pneumonia	12 (29.3%)
Vomiting	9 (22.0%)

Table 4 Characteristics of patients with Hansen's disease and COVID-19 who died

Age	Gender	Comorbidity	Hansen's disease treatment	Corticosteroids
39	F	HT/T2D/Obesity	AR	Yes
50	M	None	MDT	No
50	M	None	MDT	No
53	F	HT	MDT	No
58	M	HT	MDT	No
60	F	None	MDT	No

Abbreviations: AR, alternative regimen (clofazimine 100 mg/day + ofloxacin 400 mg/day); HT, hypertension; T2D, type 2 diabetes; MDT, WHO multidrug therapy (rifampicin 600 mg once per month + dapsone 100 mg/day + clofazimine 50 mg/day plus 300 mg once per month).

Discussion

In this cross-sectional study, COVID-19 co-infection did not appear to change the general clinical picture of (mostly multibacillary) HD. Since the beginning of the pandemic, there was consensus that MDT for HD should not be suspended in cases of co-infection, while case-by-case assessment was recommended for the two main drugs used for the treatment of HD reactions, prednisone and thalidomide.[9,10] Almost half of the patients in our study continued to receive systemic corticosteroids, two of whom were also receiving thalidomide. Thalidomide is an immunomodulatory drug that inhibits the expression of TNF-α and IFN-γ, affecting proinflammatory activity and interfering with the immune response of ENL. Suspension of thalidomide treatment for ENL carries a high risk of sudden exacerbation and development of severe conditions requiring hospitalization, which could further burden the public health system and expose HD patients to risk of nosocomial COVID-19 infection.

Concerns about increased frequency or severity of reactions in cases of SARS-CoV-2 and HD co-infection or continued use of immunomodulatory drugs to treat HD reactions do not appear to have materialized. Given that most of the patients in our sample had multibacillary Hansen's disease, 32% experiencing an HD reaction is entirely consistent with pre-pandemic figures, for example, 33% (63/265) of multibacillary patients in Brazil in 2013.[13] Santos Morais Junior et al. noted that COVID-19 did not appear to increase the frequency of HD reactions, which affected 33% (4/12) of co-infected HD patients and 42.3% (22/52) of non-COVID HD patients.[5] The same authors reported that use of prednisone reduced levels of IL-12B cytokine gene expression in HD patients with COVID-19 (co-infected patients had increased IL-6 and IL-12B expression compared with non-HD COVID-19 patients, but there were no differences in TNF-α, IL-10, IL-1β, IL-8, and IL-12 gene expression).[5] Two of six co-infected cases described by Arora et al. in India had persistent type 1 reactions with no change in severity during their COVID-19 illness,[6] while Saxena et al. reported a favorable outcome in a patient with severe type 2 HD reaction and COVID-19 despite continued use of corticosteroids and methotrexate.[7]

Pathophysiological and immunological interactions between *M. leprae* and SARS-CoV-2 have not been elucidated but may share some clinical signs.[5] *M. leprae*, by invading the nasal mucosa of the individual, can compromise the olfactory bulb in the early stages of the disease, causing olfactory dysfunction and a reduction in the volume of the olfactory bulb, triggering hyposmia or anosmia.[14] Anosmia was a clinical sign reported by 45% of patients infected with SARS-CoV-2 in a serological survey conducted in Brazil[15] consistent with the worldwide prevalence in COVID-19 of 38%.[16] In our study, 85% of co-infected patients reported anosmia. Thus, anosmia by itself could lead to confusion in the initial diagnosis of both diseases.

An early pandemic hypothesis was whether clofazimine might have a protective effect against the severity of SARS-CoV-2 infection. Clofazimine demonstrated *in vitro* activity against SARS-CoV-2 by inhibiting viral spike glycoprotein-mediated cell fusion and viral helicase activity[17] and, in a hamster model, reduced expression of IL-6, TNF-α, and CCR4, suggesting a potential to reduce the cytokine storm that can occur in COVID-19.[17] It also exhibited synergistic effects with remdesivir in reducing viral load and virus shedding from the upper respiratory tract and preventing the spread of virus replication from bronchial epithelial cells to diffuse alveolar areas.[17] All our Hansen's disease patients who died were receiving clofazimine for at least 60 days before their COVID-19 illness, but we are clearly unable to draw any conclusions as to whether the drug might have any effect on COVID-19 outcomes.

It is not yet known whether the incidence and severity of COVID-19 have been greater or less in persons affected by

Hansen's disease compared with people of comparable age and gender in the general population in countries where Hansen's disease is endemic (80% of cases of Hansen's disease worldwide occur in India, Indonesia, and Brazil). A prospective study from Brazil over 14 months from March 2019 to May 2020 showed persons with active HD had a higher risk of COVID-19 than a control group because HD patients were more likely to have household contact with a COVID-19 case.[8] We are unable to draw conclusions or make generalizations based on the observed COVID-19 mortality among our study participants (6/41 = 15%) or among all Hansen's disease patients at the five study sites (6/70 = 9%). We note that half of those who died had high blood pressure and one patient was also obese with type 2 diabetes, all of which are known risk factors for adverse COVID-19 outcomes. Of four co-infected patients who died, as reported by Santos et al., two had hypertension of whom one also had diabetes.[4] As in our study, one of the Santos et al. patients who died was a relatively young (age 39 years) woman, albeit without any comorbidities, unlike our younger female patient who died. The rollout of vaccination against COVID-19 in Brazil means that similar studies are unlikely to be repeated, and future studies will need to focus on whether persons affected by Hansen's disease are sufficiently protected by immunization.

Perhaps the most important aspect of COVID-19 that demands resources and ongoing research is the impact of the pandemic on provision of healthcare and treatment for persons affected by Hansen's disease and on public health programs to detect new cases and ensure prompt diagnosis. Our study showed that a significant proportion of patients ceased treatment, compounding an existing problem with the centralized global supply of WHO-MDT.[18] Whether this discontinuation of treatment exceeds normal levels (adherence to treatment was 83% in patients newly diagnosed with leprosy registered in the 100 Million Brazilian Cohort from 2007 to 2014),[19] whether it can be generalized across Brazil or to other countries (some reported limited impact of the initial phase of the pandemic on Hansen's disease services),[20] and whether it will adversely affect outcomes in patients requires longer term follow-up. Treatment adherence and cure among multibacillary patients was positively associated with receipt of the Programa Bolsa Família (PBF),[19] a Brazilian conditional cash transfer program which has been threatened by the financial and political fallout arising from the pandemic. Hansen's disease control in Brazil is also threatened by a precipitous fall in new case detection rates, estimated to be almost 50% nationally when comparing the average number of newly diagnosed cases in 2010–2019 with 2020, representing almost 20,000 missed cases even before taking into account cases missed during 2021.[21]

In conclusion, while the wider impact of the pandemic on healthcare for persons affected by Hansen's disease, including interruption of WHO-MDT treatment, gives cause for concern and requires close patient-level follow-up and enhanced population-level monitoring, much of the interaction, if any, between *M. leprae* and SARS-CoV-2 infection (or between active Hansen's disease and COVID-19), remains to be elucidated. Our observations are consistent with COVID-19 co-infection not changing substantially the general clinical picture of multibacillary HD or requiring changes to ongoing treatments for HD and HD reactions. The rollout of COVID-19 vaccination programs has shifted the focus to ensure that persons affected by Hansen's disease are protected now and in the future and to verify the efficacy of SARS-CoV-2 vaccines in patients with Hansen's disease. In the meantime, national Hansen's disease programs will need to plan and be sufficiently resourced to conduct catch-up campaigns to mitigate for cases and contacts missed during the pandemic.

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