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Direct and indirect effects of the SARS-CoV-2 pandemic on Gaucher Disease patients in Spain: Time to reconsider home-based therapies?

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ABSTRACT

Objective: An analysis of the SARS-CoV-2 pandemic impact in the Spanish Gaucher Disease (GD) community is presented here.
Patients & methods: The Spanish GD foundation (FEETEF) surveyed 113 GD patients from March 30 to April 27; all patients provided a verbal consent.
Results: 110 surveys were analyzed. The median age was 47 years old (y.o.), 31 patients were ≥ 60 y.o.; and 34% of patients reported comorbidities. 46% (51/110) of patients were treated by enzyme replacement therapy (ERT), 48 of them at hospitals; 45.1% (45/110) were on substrate reduction therapy (SRT) and 9% (10/110) receive no therapy. 25% (11/48) of ERT-hospital-based patients reported therapy interruptions, while SRT-patients did not report missing doses. No bone crises were reported. However, 50% (55/110) of patients reported being worried about their predisposition to a severe SARS-COV-2 infection and 29% (16/55) of them took anxiolytics or antidepressants for this. While 6 patients reported to have contact with an infected person, another two confirmed SARS-CoV-2 infections were reported in splenectomyzed patients, one of them (a 79-year-old diabetic) died.
Conclusions: One quarter of the patients treated at hospitals reported dose interruptions. Home-based therapy may need to be considered in order to minimize the impact of the COVID-19 pandemic.

1. Introduction

Gaucher disease (GD; MIM#23800, MIM#230900, MIM#231000), is the most common lysosomal storage disorder worldwide. In Spain it has an estimated incidence of 1 in 110,000 to 140,000 inhabitants [1] [2]. The therapy for GD in Spain follows the guidelines provided by the health department. There are 4 available therapies, 2 enzyme replacement therapy (ERT) options in first-line indication: Velaglucerasa alfa (Takeda Pharmaceutical) and Imiglucerase (Sanofi-Genzyme), one substrate reduction therapy (SRT), also in first-line indication, Eliglustat (Sanofi-Genzyme) and one SRT in second-line indication, Miglustat (Johnson & Johnson). Patients receive ERT at hospitals' infusions center (hospital-base-ERT) or at home (home-base-ERT), and both SRT drugs are supplied by hospitals' pharmacies.

The 14th March 2020, the Spanish Government declared a State of Alarm in Spain, in order to control the effects of the SARS-CoV-2 pandemic [3]. By May 31, more than 239,000 persons had been infected and 27,127 had died. During the State of Alarm all hospitals in the country were under the control of the Spanish Government, and substantial efforts were made to prioritize assistance for patients affected by SARS-COV-2; isolation measures and a general lockdown were also declared.

Concerning to analyze the impact of SARS-CoV-2 pandemic in GD patients, the Spanish Gaucher Disease Foundation (FEETEG) and the Spanish Association of patients and families affected by GD (AEEFEG) collaborated in a survey project. The results are presented here.

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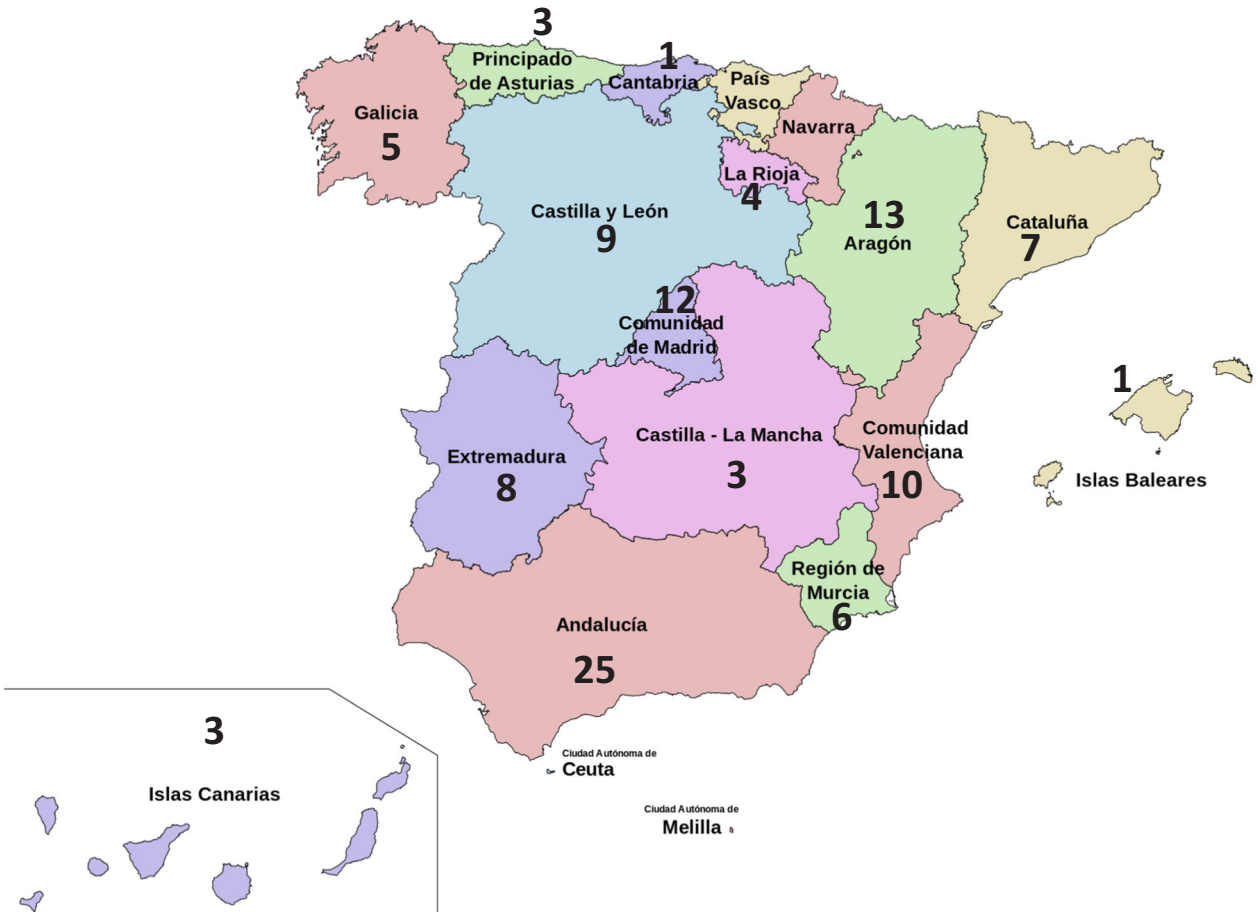

Fig. 1. Distribution of the surveyed patients within Spanish Autonomous Communities.
From left to right and from top to down: Galicia: 5 cases; Asturias: 3 cases, Pais Vasco: 1 case; Castilla y León: 9 cases; La Rioja: 4 cases, Aragón 13 cases; Cataluña 7 cases; Madrid 12 cases; Castilla La Mancha 3 cases; Valencia 10 cases; Extremadura: 8 cases; Andalucía: 25 cases; Murcia: 6 cases; Islas Baleares: 1 cases, Islas Canarias 3 cases.

Table 1
General characteristics and therapies.

General characteristics	
Gender	N (%)
Male/Female	55/54 (50.5%/49.5%)
Groups of age	
> 60 years	31 (28.2%)
50–59 years	24 (21.8%)
40–49 years	18 (16.4%)
30–39 years	8 (7.3%)
20–29 years	11 (10%)
< 20 years	22 (20%)
Genotypes for GD1 (n = 104)	
N370S/N370S: [p.Asn409Ser] + [p.Asn409Ser]	12 (11%)
N370S/L444P: [p.Asn409Ser] + [p.Leu483Pro]	45 (41%)
N370S/other [p.Asn409Ser] + [other]	40 (36%)
Other/other: [other] + [other]	13 (12%)
Therapies	
Enzymatic Replacement Therapy (ERT)	51 (46%)
Home-based ERT	6 (12%)
Hospital-based ERT	44 (88%)
Substrate Reduction Therapy	49 (45%)
No therapy	10 (9%)

ERT: enzyme replacement therapy; SRT: substrate reduction therapy.

2. Methods

2.1. Survey and statistical analysis

A customized survey available in supplemental material was created. The survey was performed by phone call, from March 30 to April 27, 2020; all patients provided a verbal consent. General demographic and clinical data at diagnosis were provided by the SGDR and a special database included the baseline information and the survey information created for this study. Descriptive analysis, frequency distribution of variables and comparative test were performed.

3. Results

3.1. Patient characteristics

114 patients were contacted and 110 (97%) accepted to participate. The majority were located in Andalucia (25/110, 23%), Aragón (13/110, 12%), Madrid (12/110, 11%), Valencia (10/110, 9%) and Castilla León (9/110, 8%) (Fig. 1). The median age of the surveyed cases was 47 years (range 3–84), and gender distribution was almost equal (56/110; 51% males and 54/110; 49% females). Most of patients, 104/110 (95%) were type 1 (GD1) and only six cases (5%) were type 3 GD (GD3). Regarding the *GBA* (MIM*606463) analysis, the most common genotype in GD3 patients was NP_000148.2:[p.Leu483Pro] + [p.Leu483Pro], while in GD1 the most common genotype was NP_000148.2:[p.Asn409Ser] + [p.Leu483Pro] (43/104;

41%), Table 1.

In regard to therapies, 51 (46.5%) patients received ERT; 6 in a home-based ERT system and the rest at their hospitals. 49 (44.5%) cases received SRT, the majority of them eliglustat (41, 37%). Finally, 10 (9%) currently receive no therapy. (Table 1).

3.2. Comorbidities and GD situation before COVID-19 pandemic

More than 45% of patients were older than 50; of all included patients, 38/110 (34%) suffer at least one comorbidity, of which arterial hypertension is the most common (19/110; 17%); chronic obstructive pulmonary disease (7/110, 6%), cancer (7/110, 6%) and diabetes mellitus (5/110; 5%) were also reported. Concomitant treatments were frequent, with medical prescription, and 56/110 (51%) of the cases reported the intake of at least one medicine different from GD therapy.

Splenectomy was common in our series, affecting 21/110 (19%) patients; 31 (28%) patients, of whom 7 were splenectomized, also reported suffering skeletal pain in the last month; none of the surveyed patients declared any diagnosis of pulmonary hypertension, but 15/110 (13%) of them were former or current smokers.

3.3. Impact of the SARS-CoV-2 pandemic

During the State of Alarm, no hospital has declared a shortage of GD therapy. When asking the patients if they were in contact with anyone confirmed to be COVID-19 positive, 6 patients respond in the affirmative; they were located in Madrid, Aragón, Extremadura, Castilla-Leon, Galicia and Castilla-La Mancha.

Two other positive SARS-CoV-2 cases were registered, both of them patients previously splenectomized. One was a 79-year-old GD1 patient who developed a severe SARS-CoV-2 infection; he did not receive specific GD therapy. The patient reported being in contact with COVID-19 affected patients and developed fever and dyspnea in mid-March; he was admitted to a Hospital in Madrid but died due to bilateral pneumonia and multiorgan failure one week later. Among his comorbidities, he had diabetes, hypertension, cured kidney cancer and was recently diagnosed with Alzheimer's disease.

The second case was a 69yo GD1 female patient, who not reported contact with any person known to be affected by COVID-19. She developed a mild SARS-CoV-2 infection with fever lasting 10 days, cough and fatigue; the X-ray did not show pneumonia and she did not require hospital admission.

From the rest of the patients, those receiving SRT reported that they do not have problems with the treatment supply and confirmed a good adherence to the therapy without missing doses. Two of the home-based ERT patients reported a minimum change in their scheduled doses, but no missing doses were registered. However, of the patients receiving ERT at hospitals, 11/44 (25%) reported that they missed several doses due to rescheduling and reorganization of their hospital infusion center. Of these, 5/11 missed one dose, 5/11 two doses, and 1/11 missed three doses of ERT. None of the surveyed cases reported to have a bone crisis or acute bone pain during the reviewed period.

During this time, 55/110 (50%) patients reported anxiety and worry about their predisposition toward infection and the possibility of developing more complications with SARS-CoV-2 infection than might non-GD patients. Also, 16/55 (29%), reported the intake of anxiolytic or antidepressant drugs for this reason.

From all the surveyed population, 86/110 (78%) were active workers; of them 34 (40%) were continuing to work at their usual workplaces, while 5 (6%) were working remotely.

4. Discussion

In the present study, an analysis of the impact of SARS-CoV-2 in the Spanish Gaucher Disease community is presented; this is a collaboration between FEETEG and AEEFEG, focused on assessing problems faced by patients during these extraordinary times. More than a quarter of the current GD cases included in the SGDR were surveyed, with representation of patients from 15 of the 17 autonomous communities in Spain. From an analysis of this survey, we can confirm that this time of pandemic is affecting the normal functioning of hospitals, impacting all patients who need health assistance and not only those directly affected by COVID19. All GD patients received their therapy from hospitals, while patients receiving oral therapy continue to receive their treatment even during the lockdown; patients receiving intravenous therapy needed to change their schedule while 25% of the patients receiving the ERT at hospitals missed doses. There was no bone crisis during this short time; 2 patients developed a confirmed SARS-CoV-2 infection and, unfortunately, one died. The impact of the COVID19 pandemic on social and psychological well-being was important among the surveyed GD patients, with half of them reporting stress and anxiety with almost one third of them needing anxiolytic or antidepressants for this reason.

In Spain, the SARS-COV-2 pandemic is having a huge impact; until May 30, Spain is the country with the 5th-highest number of cases with a confirmed infection and the 6th-highest number of deaths, with a mortality rate of ~11%. To compare the incidence of confirmed cases of COVID19 in Spain (data provided by Spanish Coordination Centre for Health Alerts and Emergencies) at 31st May 2020 the cumulative incidence per 100,000 inhabitants was 0.27%. The estimated prevalence of IgG antibodies to SARS-CoV-2 in the Spanish population is 5.21%, according to preliminary data from the second round of the ENE-Covid19 study, promoted by the Ministry of Health, supported by the Ministry of Science and Innovation and coordinated by the Carlos III Health Institute [4].

In our cohort of GD patients, the incidence has been 1.81%, but in all 110 GD patients the prevalence of IgG antibodies has not been determined so this data should be considered with caution. According the information from the Spanish Society of Hematology, the incidence of SARS-CoV-2 in patients with chronic hematological malignancies is no different from that of the general population and is estimated about 0.37%. [5]

The lessons learned from experiences in China [6] [7], Italy and New York [8] mention that patients with comorbidities – especially cardiovascular disease – are at a higher risk of complications. Regarding GD, there are no data pertaining to their predisposition to SARS-CoV-2 infections; however, it can be noticed that untreated GD patients usually showed a proinflammatory cytokine profile with a high level of IL-4, IL-6 and IL-13, and also MIP1a [9] [10], and this improves with therapy. In the infected cases reported here, both of them had undergone spleen removal, were over 65 y.o., and have comorbidities that can play a role in the fatal outcome of our cases, according to previous experiences [4] [11]. Patients with other chronic illnesses are also at risk of worsening their condition due to the pandemic's collateral effects such as the delay of therapy [12].

In 2009, a worldwide ERT shortage crisis occurred due to problems in the enzyme production; that period lasted more than 6 months and many patients experience a reduction on their infusions with some cases receiving no therapy at all. In Spain, patients who reduced their infusion up to 50% or suspended, experienced bone crisis, bone pain, anaemia, thrombocytopenia with an increase in the biomarkers. The actual situation [13], fortunately, has not exceeded 3 months and its impact is less dramatic; however, the social impact and the fear of recurrence hurry us to thing in strategies to avoid therapy interruptions for our patients.

Recent guidelines published by Mistry P et al. in the USA for the management of GD patients in SARS-CoV-2 infection emphasize that there is insufficient information to ensure that these patients are at increased risk of acquiring the infection, although the coronavirus appears to affect lysosomal function and the inflammatory status of the GD could facilitate the autoinflammatory cascade. The need to perform surveillance in patients with GD and to obtain epidemiological data in different countries is prioritary in order to establish optimal

management of the disease. In general, they recommend adherence to the guidelines of the Center for Disease Control and to take into consideration the individual characteristics in each patient [14].

Regarding lysosomal storage disorders (LSD), an Italian experience of the impact of SARS-CoV-2 in assessing different LSD patients was recently published; they included 44 treated GD patients. They also found that patients receiving oral therapy did not suffer problems with the medicine supply; one of the 16 LSD patients receiving ERT in a home-based manner missed one dose and 49% of the patients receiving therapy at hospitals experienced a treatment disruption [15]. All of this was similar to our findings. It is necessary to remark that splenectomy in GD patient needs to be avoided, and those patients who undergo it need to receive appropriate vaccination and education about infections in order to diminish their risk of infectious complications.

In conclusion, our findings support the idea that new ways to ensure continued therapy for GD patients, during a time of social disruption, such as the State of Alarm for COVID-19, need to be evaluated. It seems that home-based therapies (such as oral or home-delivery ERT) need to be reconsidered for these patients, of whom the majority usually received the therapy at hospitals. At present, the data is too scanty to make conclusions about whether GD patients are at higher risk for SARS-CoV-2 infection and complications; nevertheless, consensus guidelines will be desirable.

Conflict of interest

All the authors confirm there is no conflict of interest to declare.

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Disclosures

All authors declare that there are no conflicts of interests.
All authors have read and approved the manuscript.
This manuscript is not under consideration elsewhere.

CRediT authorship contribution statement

Marcio Andrade-Campos:Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.**Beatriz Escuder-Azuara**:Methodology, Data curation, Software.**Laura López de Frutos**:Formal analysis.**Irene Serrano-Gonzalo**:Formal analysis.**Pilar Giraldo**:Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bcmd.2020.102478.

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