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BRIEF REPORT

COVID-19 in Cushing disease: experience of a single tertiary centre in Lombardy

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Coronavirus Disease 2019 (COVID-2019) has become a world-wide public health concern that severely affected Italy and especially the region of Lombardy, where a cumulative incidence of virologically-confirmed cases of 0.6% was registered by mid-April [1]. However, in this region, the rhinopharyngeal swab has been mostly performed in severely symptomatic patients referring to Emergency Rooms, thus the precise number of cases is unknown. The estimated prevalence of the novel coronavirus infection based on at least one suggestive clinical manifestation, as at early April 2020, was 19.6% [2]. Although the influenza season was ended by mid-March, at least part of the symptoms may be not COVID-19 related and, even assuming that only half are, we can presume that at least 10% in Lombardy has been affected and symptomatic. A poor prognosis of COVID-19 defined by death, invasive ventilation, or admission to Intensive Care Unit is associated to concomitant medical conditions such as hypertension and diabetes mellitus [3], comorbidities that are frequently observed in Cushing Syndrome (CS). In addition, active hypercortisolism is a known predisposing factor for infection [4]. The principal cause of endogenous CS is Cushing Disease, a rare condition with a prevalence close to 40 cases per million inhabitants [5].

In the present study we investigated the presence of typical signs and symptoms of COVID-19 and virologically confirmed disease among 61 patients with CD and 61 controls with pituitary microincidentalomas and normal pituitary function living in Lombardy and actively followed at Ospedale Maggiore Policlinico in Milan, Italy. The first group included all the patients with confirmed CD that underwent at least one endocrinological evaluation during the last 12 months at our centre. We performed a telephone inquire that included information related to influenza vaccination, risky behaviours for COVID-19 (smoking, work, travel, cohabitants number), suggestive clinical features (fever, cough, dyspnoea, anosmia, ageusia, conjunctivitis, diarrhoea, tiredness) and COVID-19 testing, from January to mid-April 2020. All the contacted patients responded to the telephone call.

The CD group included 15 cases of active hypercortisolism, 28 patients in remission with hypoadrenalism and 18 eucortisolemic subjects. The two groups had the same mean age and gender distribution (CD 52.6 ± 12.4, controls 52.7 ± 11.7 years, female percent 83.3% in both groups). The presence of risky behaviours and influenza vaccination rate were similar in the two groups (Table 1).

We found two cases (3.2%) of virologically confirmed COVID-19 in CD patients, but none in the control group. The first patient was a 55-year old woman in remission, with hypoadrenalism adequately treated, end-stage chronic kidney disease, and malnutrition. She was admitted in the Pulmonary Unit and treated with hydroxychloroquine, Continuous Positive Airway Pressure and hydrocortisone continuous infusion 200 mg/24 h. Unfortunately, she died after 6 days of hospitalisation. The second, a 71-year old man with active hypercortisolism, obesity, hypertension, dyslipidaemia who discontinued metyrapone one month before because of gastrointestinal disturbances; his general state improved after one week of isolation in a non-medical structure.

Because of the small number of patients tested by nasopharyngeal swab for COVID-19 both in Lombardy (221.968/10.000.000) [1] and in our population (5/122), we also investigated the presence of characteristic signs and symptoms. Overall, almost 38% of CD and 47% of controls had at least one clinical feature between January and mid-April. Considering a more specific clinical presentation as the association of fever and dry cough with other symptoms,

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Table 1 Characteristic of patients with Cushing disease and microincidentaloma in the context of COVID-19 pandemic

	Cushing disease $N=61$	Controls $N=61$
Age (years)[a]	52.6 ± 12.4	52.7 ± 11.7
Females	51 (83.3%)	51 (83.3%)
Smoking	8 (13.1%)	11 (18%)
Influenza vaccination	20 (32.7%)	16 (26.3%)
Profession at risk	10 (16.4%)	7 (11.5%)
Daily travel for work	8 (13.1%)	7 (11.5%)
Use of public transportation	2 (3.2%)	2 (3.2)
N° of cohabitants[b]	1 (0–5)	2 (0–5)
N° cases SS[c] + : Jan to 15 Apr	23 (37.7%)	29 (47.5%)
N° cases SS + : Mar to 15 Apr	9 (14.7%)	15 (24.6%)
N°SS: Mar to 15 Apr	3 (1–7)	2 (1–6)
Cough and fever	4 (6.5%)	1 (1.6%)
At least 3 SS for 1 week min	4 (6.5%)	2 (3.2%)
Nasopharyngeal swab	2 (3.2%)	3 (4.9%)
COVID-19 +	2 (3.2%)	0

[a]Mean ± Standard deviation

[b]Median (range)

[c]Signs and symptoms

lasting for at least one week between March and mid-April (when influenza was unlikely), we found four CD patients and one subject with pituitary microincidentaloma. Three of four CD patients had active hypercortisolism: one patient had persistent CD after pituitary surgery and two were newly diagnosed CD patients waiting for surgical treatment.

Our survey was conducted on a relatively small cohort of CD patients with only 15 cases of active hypercortisolism that precludes statistical conclusions. Furthermore, remote assessment did not permit an objective clinical examination and therefore under- as well as over-estimation of some symptoms cannot be excluded. Nevertheless, it shows that 3.2% of CD had confirmed COVID-19 compared with 0.6% of the general population in Lombardy by mid-April [1]. Moreover, a severe clinical presentation was observed especially in patients with active CD, suggesting that chronic hypercortisolism may be associated with more serious SARS-CoV-2 infection. Overall, our data indicate that active CD patients should be considered as a fragile population.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study was approved by Milan Area 2 Ethical Committee (ID 1623). The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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