European Review for Medical and Pharmacological Sciences 2021; 25: 4400-4404

COVID-19 in celiac disease: a multicentric retrospective cohort study

G. GASBARRINI[1], T. DIONISI[1], G.R. CORAZZA[2], N. ARONICO[2], G. CAMMAROTA[1], G. IANIRO[1], I. DE VITIS[1], M. CANDELLI[1], F.A. MANCARELLA[1], S. SIMEONI[1], G. ADDOLORATO[1], F. BONVICINI[3]

[1]Institute of Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[2]First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy
[3]Institute of Medical Semeiotics, Azienda Ospedaliero-Universitaria di Bologna Policlinico S. Orsola – Malpighi, Bologna, Italy

Abstract. – OBJECTIVE: Celiac disease (CD) is an autoimmune disorder, characterized by increased susceptibility to bacterial and viral infections. Therefore, the CD patients could be exposed to an increased risk of contracting SARS-CoV-2, a virus for which the WHO declared a pandemic status in March 2020. This study aims to investigate the incidence of SARS-CoV-2 infection in CD patients, to assess the impact of CD on the risk of contracting this virus.

PATIENTS AND METHODS: This retrospective multicentric cohort study evaluated 542 celiac patients, who answered a questionnaire concerning both the underlying disease (adherence to the gluten-free diet, residual symptoms) and the possible SARS-CoV-2 infection (swab outcome, presence and characteristics of symptoms and type of treatment received), referring to the period between 20th January 2020 and 27th October 2020.

RESULTS: Five patients (0.92%) tested positive; of these, 2 were asymptomatic and 3 developed symptoms of COVID-19. The incidence of SARS-CoV-2 infection in CD patients was not significantly different from the general population. The ratio of positive/diagnostic swabs tends to be higher in CD patients than in the general population (IR: 0.15; 0.06; p=0.06), whereas the number of subjects who performed the swab in this group is significantly lower (IR: 0.06; 0.15; p<0.001).

CONCLUSIONS: Although CD patients are more susceptible to infections, the incidence of SARS-CoV-2 infection in our sample was not significantly different from the general population. However, the positive/diagnostic swabs ratio seems to be higher, probably also due to the lower number of patients tested.

Key Words:
Celiac disease, Covid-19, Epidemiology, Incidence, SARS-Cov2.

Introduction

Celiac disease (CD) is a disease related to poor tolerance for gluten, a protein contained in wheat and remarkable for its nutritional properties[1-4].

It is the most frequent food intolerance and affects approximately 1% of the population. It has been calculated that, in Italy, the theoretical number of people with CD is around 600,000, against 214,239 diagnosed to date. The disease is more frequent among women: official data indicate that 63,320 males are suffering from the CD, compared to 150,919 females[5].

Up to the present time, the most reliable therapy for the remission of the disease seems to be the abolition of gluten from the diet. Maintaining adherence to a gluten-free diet, the patients can almost completely avoid symptoms and complications, some of which can be fatal[6].

One of these complications is the ease of contracting viral[7] and bacterial infections. The latter is probably related to the "splenic hypofunction syndrome"[8-11], which could arise in conditions of extreme reduction in spleen size[12,13] or functional organ failure not necessarily associated with volumetric reduction, as in the case of replacement of the splenic parenchyma by heteroplastic tissue[14]. There are uncertain reasons why, in CD patients, viruses and bacteria can cross the intestinal mucous barrier and affect the lymphatic system, leading to an infectious syndrome with peripheral and multi-district symptoms[15]. It cannot be excluded that the gut, through which germs often enter the body, may become leaky in CD, also due to pathophysiological processes still poorly studied (unstirred layer)[16-21].

Corresponding Author: Tommaso Dionisi, MD; e-mail: tommasodionisi@libero.it

The complex picture that characterizes this disease requires an assessment of the impact of SARS-CoV-2 infection in CD patients, a virus that had already recorded over 500,000 cases at the end of October 2020 in Italy[22].

This study aims to identify the incidence, the clinical features, and the outcome of SARS-CoV-2 infection in CD patients in Italy. Secondly, it aims to compare these data with the epidemiology of SARS-CoV-2 infection in the Italian population over the same time.

Patients and Methods

This retrospective cohort study involved the Departments of Internal Medicine and Gastroenterology of Policlinico A. Gemelli in Rome (Italy), the Institute of Internal Medicine of Policlinico San Matteo in Pavia (Italy), the Institute of Medical Semeiotics of Policlinico Sant'Orsola in Bologna (Italy).

Patients were invited by e-mail, face-to-face, or direct phone call to participate. The invitation to participate explained the voluntary and confidential nature of the study.

All the recruited patients had previously received a diagnosis of CD according to the guidelines of the European Society for the Study of Coeliac Disease (ESsCD)[23] and had regularly followed at their reference centers.

These patients answered a validated questionnaire regarding both the underlying disease (adherence to the gluten-free diet, residual symptoms) and the possible SARS-CoV-2 infection (swab outcome, presence and characteristics of symptoms, and type of treatment received). The obtained information refers to the period between 20th January 2020, when the first two cases in Italy were recorded, and 27th October 2020. Patients who stayed for at least three weeks in other countries were excluded. Patients from Northern Lombardy (Italy), (provinces of Milan, Bergamo, and Varese) and Calabria were programmatically excluded from the research because in those areas the incidence of SARS-CoV-2 infection was substantially doubled compared to other regions and provinces of Italy. A total of 752 patients were contacted and 542 of them were enrolled. The regions of origin of the patients tested were: Lazio, Southern Lombardy, Emilia-Romagna, Abruzzo, Puglia, Veneto, and Sardinia (Italy). Given the epidemiological differences between the various regions of Italy[22], patients were divided into subgroups according to the reference centers, and the incidence of COVID-19 in each subgroup was compared with that of the region in which the reference center is located.

Only patients with symptoms related to COVID-19 and those who had direct contact with people positive for SARS-CoV-2 in the last 3 weeks performed a nasopharyngeal swab with molecular analysis.

To estimate the incidence of SARS-CoV-2 infection in the period of interest, in the general population, and the population related to the centers participating in the study, epidemiological data were obtained from the reports of the Istituto Superiore di Sanità and Regional Governmental sites, referring to the same period. The study was approved by the Ethical Committees of all Centers involved.

Statistics

The Stata 14 software was used for data analysis. The descriptive statistics showed the frequency and percentage for each categorical variable. The incidence of SARS-CoV-2 infection in CD patients and the general population was reported with their 95% confidence interval (CI), calculated with the Clopper-Pearson method. Relative Risk (RR) was reported. The categorical data were compared between groups using Fisher's exact test. The p-value below 0.05 was considered statistically significant in the two-tailed test.

Results

Of the 542 patients enrolled, 34 (6.3%) performed a nasopharyngeal swab for SARS-CoV-2. Of these, 5 patients (0.92%) tested positive: 2 were asymptomatic and 3 developed symptoms of COVID-19. In particular, 2 developed asthenia and sensory disturbances, and only 1 developed fever, dyspnea, asthenia, and sensory disturbances. All patients with symptoms were treated at home.

It is interesting to note that among the 5 positive patients, 3 belong to blood type 0 and 2 to blood type A. However, new investigations on this data are still in progress.

The incidence of SARS-CoV-2 infection in the study sample is 0.92% (IR, 0.009; IC 95%, 0.003-0.021). No significant difference was found between the incidence in CD patients and the incidence in the general population in the period studied, which was 0.93% (IR, 0.009; IC 95% 0.009-0.009; RR: 0.984; p=1). The same analysis

conducted by dividing the sample based on reference centers produced the same result [Policlinico Gemelli, Rome: CD 0.49% (IR, 0.005; IC 95%: 0.001-0.018); reference population 0.64% (IR: 0.006; IC 95% 0.006-0.006; RR: 0.763; p=1); Policlinico San Matteo, Pavia: celiacs 0.87% (IR: 0.009; IC 95%: 0.000-0.047); reference population 1.6% (IR: 0.016; IC 95%: 0.016-0. 016; RR: 0.537; p=1)], except for the subgroup of patients who refers to the Policlinico Sant'Orsola, Bologna, where the incidence is significantly higher than the reference population [Sant'Orsola: CD 10% (IR: 0. 1; IC 95%: 0.012-0.317); reference population 1.1% (IR: 0.011; IC 95%: 0.011-0.011); RR: 9.08; p=0.02], probably due to the lower number of patients enrolled (20; 3.7% of the sample).

The positive/diagnostic swabs ratio tends to be higher in CD patients than in the general population (CD patients: IR: 0.147; IC 95%: 0.049-0.310; general population: IR: 0.062; IC 95%: 0.062-0.062; RR: 2. 363; p=0.058). Instead, the number of subjects who performed the swab is significantly lower in this group (CD: IR: 0.063; IC 95%: 0.044-0.087; general population: IR: 0.150; IC 95%: 0.150-0.151; RR: 0.416; p=0.000).

Discussion

In this study, the incidence and clinical features of SARS-CoV-2 infection were measured in a sample of patients with CD, and we found no significant differences from the general population. Similar results were reported in the same population, both for CD patients and for patients with other autoimmune diseases[24-28].

CD patients are known to have an increased risk of infection. This could be, almost in part, related to hyposplenism, which affects about 20-80% of CD patients, leading to an increased susceptibility to infection, in particular by encapsulated bacteria (*Streptococcus Pneumoniae, Neisseria Meningitidis*, and *Haemophilus influenzae*). This condition correlates with the time of exposure to gluten[29]. Increased susceptibility to bacterial infections exposes CD patients to the risk of developing a severe form of SARS-CoV-2 infection, which can lead to death up to 50% of patients in case of co-infection[30]. The risk of developing a severe form is also related to complications of CD and the effects of immunosuppressive therapy they could undergo.

However, no patient in our sample needed hospitalization: this could be related to the prevalent adherence to the gluten-free diet of the patients, preventing the onset of hyposplenism, and other complications and limiting the use of immunosuppressants.

Besides, there is evidence that the intestinal microbiota may affect the response to respiratory viral agents, and may determine the outcome of patients with ARDS, due to a gut-to-lung bacterial translocation. Therefore, some authors have hypothesized that intestinal dysbiosis, which also occurs in CD patients, may determine a more severe form of COVID-19[31].

Moreover, CD patients are also characterized by an increased risk of viral infection, linked to the presence of HLA-DQ2, which has a reduced ability to present the antigen to CD4+ T helper lymphocytes, compromising their antiviral activity[32].

As described, CD patients are more often women and young, who are more likely to have contracted SARS-CoV-2 asymptomatically. Indeed, some studies[33,34] have shown that SARS-CoV-2 infection occurs in a symptomatic and more severe form in male and older patients. As reported by Schiepatti et al[35], even in our sample, the incidence could therefore be underestimated.

It is necessary to consider that CD patients routinely engage in behaviors that reduce the risk of exposure to SARS-CoV-2, due to the habit of avoiding social contexts, like those related to the consumption of the meal[35]. For this reason, it is interesting to note that in our sample the ratio of positive/diagnostic swabs tends to increase compared to that of the general population. Although this data cannot be conclusive, it would seem to support the hypothesis that CD patients are at greater risk of contracting SARS-CoV-2. Moreover, it appears that the number of patients who performed the swab in our sample is significantly lower than that of the general population. This may be due to CD patients' lack of perception of the increased risk of infection[36]. This may have led to an underestimation of SARS-CoV-2 positive patients, and an overestimation of the percentage of symptomatic patients, since potentially positive but untested patients would have been classified as asymptomatic.

This study has several limitations, mainly related to its observational nature. Moreover, the demographic features of the sample are different from those of the general population, making the interpretation of some results problematic. The number of patients provided by the three centers that participated in the study is very different, and this may have led to an error in the total incidence

calculated, also due to the different spread of the virus in the Italian regions. Besides, during the first pandemic wave, a few swabs were performed, because of the reduced resources, making the incidence calculated largely underestimated.

The sample size is not sufficient to identify statistically significant differences, given the low number of SARS-CoV-2 positive cases in the study group.

Conclusions

Although CD patients have a higher susceptibility to some infections, both due to immune alterations and gut-lung axis, and therefore they have the risk of presenting COVID-19 disease in a severely evolving form, the incidence of SARS-CoV-2 infection in our sample of CD patients was not significantly different from the general population. Furthermore, according to our case series, CD patients who were affected by COVID-19 disease always developed an oligosymptomatic clinical picture. The positive/diagnostic swabs ratio seems to be higher than the general population, also due to the lower number of patients tested, probably.

Further studies, with higher sample size, will be necessary to determine the incidence of SARS-CoV-2 in CD patients and to define the genetic (i.e., blood groups), immunological (with related systemic symptoms), and clinical (severity and evolution) characteristics of the infection and related factors.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) French JM, Hawkins CF, Smith N. The effect of a wheat-gluten free diet in adult idiopathic steatorrhoea – a study of 22 cases. Quart J Med 1957; 26: 481-499.
2) Corazza GR, Frisoni M, Valentini R, Barnabeo RA, Gasbarrini G. Jacomo Bartolomeo Beccari and the discovery of gluten; in Kumar PJ, Walker-Smith JA (eds): Coeliac Disease: One Hundred Years. London, St Bartholomew's Hospital, 1988; 11-14.
3) Ciccocioppo R, Di Sabatino A, Corazza GR. The immune recognition of gluten in coeliac disease. Clin Exp Immunol 2005; 140: 408-416.
4) Losowsky M. A History of coeliac disease. Dig Dis 2008; 26: 112-120.
5) Ministero della Salute. Direzione Generale per l'Igiene e La Sicurezza Degli Alimenti e La Nutrizione Relazione Annuale Al Parlamento Sulla Celiachia, Anno 2018.
6) Gasbarrini, G, Mangiola F. Wheat-related disorders: a broad spectrum of 'evolving' diseases. United Eur Gastroent J 2014; 2: 254-262.
7) Abenavoli L, Proietti I, Vonghia L, Leggio L, Ferrulli A, Capizzi R, Mirijello A, Cardone S, Malandrino N, Leso V, Rotoli M, Amerio PL, Gasbarrini G, Addolorato G. Intestinal malabsorption and skin diseases. Dig Dis 2008; 26: 167-174.
8) Corazza GR, Gasbarrini G. Coeliac disease in adults. Baillieres Clin Gastroenterol 1995; 9: 329-350.
9) Logan RF, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology 1989; 97: 265-271.
10) Dameshek W. Hyposplenism. JAMA 1955; 157:613.
11) Bullen AW, Hall R, Gowland G, Rajah S, Losowski MS. Hyposplenism, adult coeliac disease, and autoimmunity. Gut 1981; 22: 28-33.
12) Corazza GR, Bullen AW, Hall R, Robinson PJ, Losowsky MS. Simple method of assessing splenic function in coeliac disease. Clin Sci (Lond) 1981; 60: 109-113.
13) Corazza GR, Frisoni M, Vaira D, Gasbarrini G. Effect of gluten-free diet on splenic hypofunction of adult coeliac disease. Gut 1983; 24: 228-230.
14) Di Sabatino A, Rosado MM, Miele L, Capolunghi F, Cazzola P, Biancheri P, Carsetti R, Gasbarrini G, Corazza GR. Impairment of splenic IgM-memory but not switched-memory B cells in a patient with celiac disease and splenic atrophy. J Allergy Clin Immunol 2007; 120: 1461-1463.
15) Corazza GR, Frisoni M, Vaira D, Gasbarrini G. Fatal pneumonia in a patient with coeliac disease and splenic atrophy. Ital J Gastroenterol 1984; 16: 300-301.
16) Levitt MD, Kneip JM, Levitt DG. Use of laminar flow and unstirred layer models to predict intestinal absorption in the rat. J Clin Invest 1988; 81: 1365-1369.
17) Levitt MD, Julie KF, Levitt DG. Shaking of the intact rat and intestinal angulation diminish the jejunal unstirred layer. Gastroenterology 1992; 103: 1460-1466.
18) Strocchi A, Levitt MD. A reappraisal of the magnitude and implications of the intestinal unstirred layer. Gastroenterology 1991; 101: 843-847.
19) Strocchi A, Levitt MD. Role of villous surface area in absorption science versus religion. Dig Dis Sci 1993; 38: 385-387.
20) Strocchi A, Corazza G, Furne J, Fine C, Di Sario A, Gasbarrini G, Levitt MD. Measurements of the jejunal unstirred layer in normal subjects and patients with celiac disease. Am J Physiol-Gastr L 1996; 270: G487-G491.

21) Ciccocioppo R, Finamore A, Ara C, Di Sabatino A, Mengheri E, Corazza GR. Altered expression, localization, and phosphorylation of epithelial junctional proteins in celiac disease. Am J Clin Pathol 2006; 125: 502-511.

22) Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19, Aggiornamento nazionale: 7 novembre 2020.

23) Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, Mulder CJ, Lundin KEA. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United Eur Gastroent J 2019; 7: 583-613.

24) Zingone F, D'Odorico A, Lorenzon G, Marsilio I, Farinati F, Savarino EV. Risk of COVID-19 in celiac disease patients. Autoimmun Rev 2020; 102639.

25) Emmi G, Bettiol A, Mattioli I, Silvestri E, Di Scala G, Urban ML, Vaglio A, Prisco D. SARS-CoV-2 infection among patients with systemic autoimmune diseases. Autoimmun Rev 2020; 19: 102575.

26) Siniscalchi M, Zingone F, Savarino EV, D'Odorico A, Ciacci C. COVID-19 pandemic perception in adults with coeliac disease: an impulse to implement the use of telemedicine. Dig Liver Dis 2020; 52: 1071-1075.

27) Negri E, Scarpino V, La Vecchia C. Prevalence of COVID-19-like symptoms in Italy and Lombardy, March-April 2020, and their implications on cancer prevention, diagnosis and management. Eur J Cancer Prev 2021; 30:1 23-125.

28) Zhen J, Stefanolo JP, Temprano MP, Tedesco S, Seiler C, Caminero AF, de-Madaria E, Huguet MM, Vivas S, Niveloni SI, Bercik P, Smecuol E, Uscanga L, Trucco E, Lopez V, Olano C, Mansueto P, Carroccio A, Green PHR, Day A, Tye-Din J, Bai JC, Ciacci C, Verdu EF, Lebwohl B, Pinto-Sanchez MI. The risk of contracting COVID-19 is not increased in patients with celiac disease. Clin Gastroenterol Hepatol 2021; 19: 391-393.

29) Elli L, Scaramella L, Lombardo V, Scricciolo A, Doneda L, Roncoroni L, Vecchi M. Refractory celiac disease and COVID-19 outbreak: Findings from a high incidence scenario in Northern Italy. Clin Res Hepatol Gastroenterol 2020; 44: e115-e120.

30) Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? J Microbiol Immunol Infect 2020; 53: 505–512.

31) Scaldaferri F, Ianiro G, Privitera G, Lopetuso LR, Vetrone LM, Petito V, Pugliese D, Neri M, Cammarota G, Ringel Y, Costamagna G, Gasbarrini A, Boskoski I, Armuzzi A. The thrilling journey of SARS-CoV-2 into the intestine: from pathogenesis to future clinical implications. Inflamm Bowel Dis 2020; 26: 1306-1314.

32) Jabri B, Sollid LM. T Cells in celiac disease. J Immunol 2017; 198: 3005-3014.

33) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.

34) Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323: 1775-1776.

35) Schiepatti A, Alimenti E, Maimaris S, Nicolardi ML, Manzella La Barbera F, Baiardi P, Biagi F. Prevalence, incidence and clinical features of SARS-CoV-2 infection in adult coeliac patients. Eur J Gastroenterol Hepatol. 2021 Jan 4; Publish Ahead of Print. doi: 10.1097/MEG.0000000000001969. Epub ahead of print.

36) Ciacci C, Zingone F. The perceived social burden in celiac disease. Diseases 2015; 3: 102-110.