## Autoimmune hepatitis after coronavirus disease vaccination

**To the Editor,**

A 21-year-old girl, without significant medical history, developed dizziness, loss of appetite, nausea, and vomiting one day after receiving the first dose of Sinopharm vaccine for coronavirus disease 19 (COVID-19). On the fourth day after vaccination, she developed jaundice with darken urine. Based on the laboratory findings [total bilirubin=7.8 mg/dL, direct bilirubin=4.6 mg/dL, aspartate transaminase (AST)=429 U/L, alanine aminotransferase (ALT)=1700 U/L, and alkaline phosphatase (ALP)=373 U/L], a family physician referred the patient to our center.

The patient had no history of using drugs or herbal medicines in the last three months. She did not travell in the last six months and had no history of surgery, jaundice, or blood transfusion, no family history of liver problems or jaundice, and no complaints upon admission. The physical examination showed normal findings, except for jaundice. Complete blood cell count and serum urea, creatinine, and glucose levels were normal on the day of admission. The results of liver function tests were as follows: AST=130 U/L, ALT=470 U/L; ALP=850 U/L; total bilirubin=13.8 mg/dL and direct bilirubin=11.2 mg/dL. Ceruloplasmin, urine copper, serum copper, iron, alpha-1 antitrypsin, and serum IgA and IgM levels, were normal. The results of anti-mitochondrial antibody, anti-smooth muscle antibody, liver-kidney microsomal antibody, and anti-soluble liver antigen tests were negative. Serological tests for hepatitis B, C, and E yielded negative results. However, the antinuclear antibody (ANA) test was positive (1.2 IU/mL). The serum IgG level was 2,100 mg/dL, and hepatitis A virus (HAV) antibody (IgM) was positive (3.5 IU/mL). The color Doppler ultrasound of the abdominal arteries and ultrasound of the liver, gallbladder, and bile ducts showed no remarkable findings.

Considering the increasing level of bilirubin, positive ANA and HAV antibodies, and increasing serum IgG levels, the patient underwent liver biopsy. The histopathological examination of the liver demonstrated lobular cholestasis and ballooning of the hepatocytes with lymphocytic and eosinophilic infiltrations (i.e., lobular hepatitis). The portal tracts showed predominant lymphocytic infiltration with a small number of plasma cells and histiocytes, as well as few eosinophils. Trichrome staining showed mild to moderate fibrosis. The Periodic Acid–Schiff (PAS) staining showed a negative reaction, and rhodamine staining indicated no copper accumulation. These findings suggested chronic active hepatitis compatible with autoimmune hepatitis. Histopathological findings are shown in Fig. 1.

According to the pathological findings, hydrocortisone therapy (100 mg every eight hours) was initiated. The reduction of liver enzymes, permitted that the patient was discharged from the hospital, and oral medications, including prednisolone (10 mg Bid), azathioprine (50 mg daily), and lactulose (10 cc, Tds.), were prescribed. The patient was advised to return for an outpatient visit to undergo periodic testing.

At one month follow-up visit the tests were completely normal; accordingly, the doses of prednisolone (10 mg daily) and azathioprine (50 mg daily) were reduced. Within three months after the disease onset, prednisolone was discontinued, as the test results remained normal. Meanwhile, HAV antibody (IgM) and ANA tests were negative, and the serum IgG level was 1,426 mg/dL.

Reports on the liver complications of COVID-19 vaccines are rare, and all cases have been attributed to mRNA vaccines, including Pfizer BioNTech, Moderna, and Oxford/AstraZeneca vaccines; this is probably due to the similarity of the virus protein with the genetic codes of these vaccines, which results is immune reactions [1-3]. The side effects of these vaccines are mild in most cases, including pain and swelling at the injection site, loss of appetite, fatigue, nausea, and vomiting [4]. Here, we reported the hepatic complications triggered by the Sinopharm vaccine. This vaccine introduces an inactivated copy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the body [5]. Although

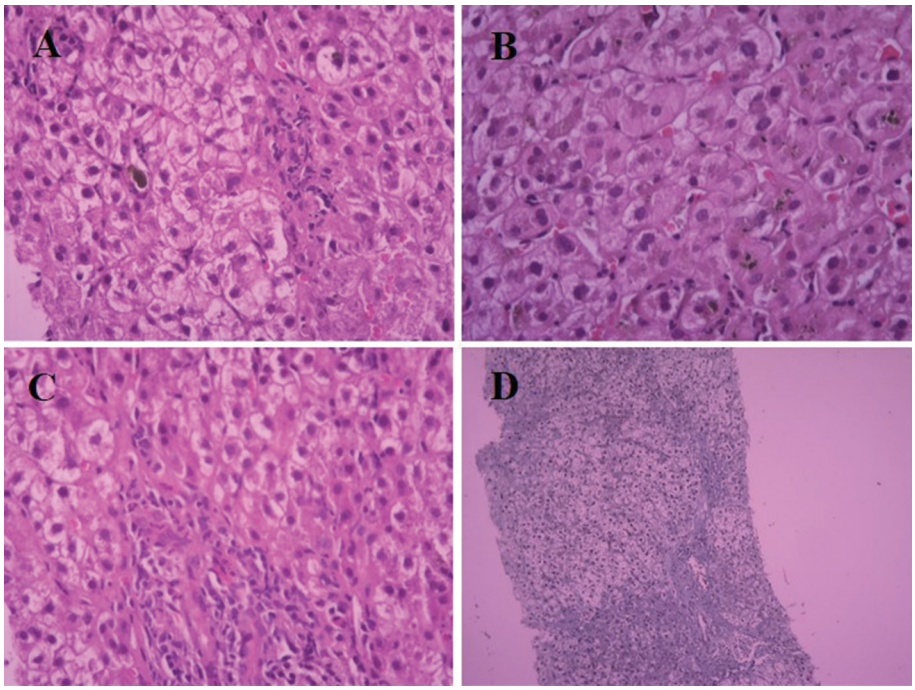


**Fig. 1**. Liver histopathological findings. A) Cholestasis: Bile pigments within hepatic parenchyma (40X magnification, hematoxylin-eosin staining). B) Lobular hepatitis: Hepatic lobules show ballooning of hepatocytes with lymphocytic and eosinophilic infiltrates (40X magnification, hematoxylin-eosin staining). C) Marked portal inflammation involving lymph plasma cells and few eosinophils (40X magnification, hematoxylin-eosin staining). D) Mild to moderate fibrosis (10X magnification, trichrome staining).

only few cases of autoimmune hepatitis have been reported following COVID-19 vaccination [6], this was the first case report of an autoimmune hepatitis after Sinopharm COVID-19 vaccination. Similar to most previous reports, our patient was also a female, but she was younger than other patients described in previous reports. Besides, the interval until the emergence of vaccine-related complications was shorter in our patient compared to previous reports.

In rare cases, COVID-19 vaccines may act as a trigger or activator of autoimmune hepatitis by stimulating the immune system; therefore, this condition should be considered in the differential diagnosis of acute hepatitis of unknown etiology.

**Omid Eslami[1], Mahdiyeh Lashkarizadeh[2]**
1) Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran; Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman; 2) Department of Pathology and Stem Cell Research Center, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

**Correspondence:** Omid Eslami, o.eslami@kmu.ac.ir

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## The impact of the COVID-19 pandemic on adherence to first-round colorectal cancer screening program: a public health issue

**To the Editor,**

Adherence to a colorectal cancer (CRC) screening program is a long-lasting challenge. Different patient- and system-level factors have been identified in the past [1], to which the negative impact of the COVID-19 pandemic should be added. Indeed, many countries temporarily suspended their cancer screening activities in the early months of the emergency [2], contributing to the idea spreading that undergoing cancer

screening can be postponed. As a result, a significant decrease in the participation rate to these programs was observed worldwide in 2020 and 2021, with consequences yet to be determined [3].

In our center, the CRC screening program was suspended for three months (March-May 2020) and was resumed in June, when all subjects not invited during the suspension period were contacted. We report data on adherence and endoscopic findings in subjects who tested positive for the fecal immunochemical test (FIT) and eventually underwent colonoscopy, comparing data from 2018-2019 (before the pandemic) to 2020-2021 (during the pandemic) and focusing on individuals who accepted to enter our program for the first time.

A total of 627 subjects with FIT-positive results at first round underwent colonoscopy during the study period (Table I). Despite a similar invitation rate, there was a distinct reduction in the number of participants during the pandemic period (455 vs. 172 subjects). This finding was associated with a significantly lower elapse time between FIT and colonoscopy in 2020-2021, with an increased percentage of subjects who underwent colonoscopy within 30 days. No other difference emerged. However, in line with the literature [4], the fecal hemoglobin concentrations were significantly higher in individuals with advanced colorectal neoplasia than in those with non-advanced neoplasia (411 vs. 241 ng/mL, p<0.001), as well as in cases with a distal lesion compared to subjects with a proximal lesion (363.5 vs. 221.5 ng/mL, p<0.001).

Our data found that the COVID-19 pandemic did not affect the quality of the endoscopic visits, despite the work-related stress of physicians during the pandemic situation. Indeed, the endoscopic performance and detection of advanced neoplastic lesions remained unchanged. In contrast, compared to previous years, fewer people entered the CRC screening program for the first time in 2020, and only a partial catch-up was observed in 2021. Reasons underlying non-adherence to CRC screening are different, including socioeconomic, ethnic and sociological influences. In addition, restrictions of mobility and fear of becoming infected with colonoscopy could have been other barriers during the COVID-19 pandemic. However, it has been demonstrated that initial participation is a predictor for continuous participation in population-based CRC screening [5]. Therefore, effective strategies aimed at restoring the importance of participating in CRC screening programs as soon as the subject become eligible should be implemented. Particularly, to minimize the long-term impact of the COVID-19 pandemic and avoid a public health crisis, we should reach out to the individuals that declined to enter the program for the first time in 2020 and 2021 through the development of targeted initiatives aimed at improving their knowledge and awareness of the benefits of participating in CRC screening programs and by providing them logistical support.

**Paolo Fedeli[1], Antonio Sciurti[2], Angelo Zullo[3], Alessandra Sinopoli[4,5], Valentina Baccolini[2]**

1) Gastroenterology Unit. Santo Spirito Hospital, , Rome; 2) Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome; 3) Gastroenterology Unit, Nuovo Regina Margherita Hospital, Rome; 4) Department of Prevention, Local Health Unit Roma 1, Rome; 5) Department of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy

**Table I**. Demographic and clinical characteristics of the participants (N=627) by year.

| | 2018 (N = 240) | 2019 (N = 215) | 2020 (N = 48) | 2021 (N = 124) | p |
|---|---|---|---|---|---|
| Gender N, % | | | | | 0.52 |
| Female | 135 (56.3) | 116 (54.0) | 22 (45.8) | 63 (50.8) | |
| Male | 105 (43.8) | 99 (46.0) | 26 (54.2) | 61 (49.2) | |
| Age, median (IQR) | 52.1 (50.2-60.6) | 51.2 (50.4-52.4) | 50.6 (50.3-52.2) | 52.4 (50.6-53.4) | <0.001 |
| Haemoglobin concentration (ng/mL), median (IQR) | 239.5 (150-635.5) | 299 (159-791) | 273.5 (136.5-589) | 248.5 (141-513.5) | 0.21 |
| Colonoscopy finding N, % | | | | | 0.63 |
| Normal finding or non-neoplastic lesion | 191 (79.6) | 169 (78.6) | 35 (72.9) | 93 (75.0) | |
| Colorectal cancer or advanced adenoma | 49 (20.4) | 46 (21.4) | 13 (27.1) | 31 (25.0) | |
| Lesion site N, % (N =364) | | | | | 0.40 |
| Proximal colon | 23 (9.6) | 21 (9.8) | 5 (10.4) | 18 (14.5) | |
| Distal colon | 74 (30.8) | 62 (28.8) | 18 (37.5) | 42 (33.9) | |
| Lesion dimension (mm), median (IQR) (N = 364) | 9 (5-18) | 8 (5-15) | 10 (5-15) | 10 (3.5-12) | 0.83 |
| Days elapsed from the FIT to colonoscopy, median (IQR) (N = 624) | 52 (36-74.5) | 40 (27-54) | 35 (20.5-45) | 47 (34-77) | <0.001 |
| Colonoscopy completion N, % | | | | | 0.93 |
| Complete | 229 (95.4) | 206 (95.8) | 45 (93.8) | 119 (96.0) | |
| Incomplete | 11 (4.6) | 9 (4.2) | 3 (6.3) | 5 (4.0) | |
| Positive predictive value, % (95% CI) | 20.4 (15.5-26.1) | 21.4 (16.1-27.5) | 27.1 (15.3-41.9) | 25.0 (17.7-33.6) | 0.63 |
| Proportion of subjects undergoing colonoscopy within 30 days from FIT positivity, % (95% CI) | 14.6 (10.4-19.7) | 31.2 (25.0-37.8) | 41.7 (27.6-56.8) | 20.2 (13.5-28.3) | <0.001 |

IQR: interquartile range; FIT: faecal immunochemical test; CI: confidence interval. Chi-square test was used for categorical data and Kruskal-Wallis test was used for continuous data.

**Correspondence:** Paolo Fedeli paolo.fedeli@aslroma1.it

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## Ageing and comorbidities in humans with antigliadin antibodies

**To the Editor,**

We read with interest the paper *Clinical Relevance of Anti-Gliadin Seropositivity in the Ageing Population: A Long-term Follow-up Study* by Ruuskanen et al. [1] recently published in your journal. The authors reviewed the medical records of human subjects with antigliadin antibodies (AGA) during long term follow-up. They evaluated 182 subjects aged 64-88 years (median 76 years) who were AGA-positive or negative after more than 12 years from the first AGA assessment. Only 1 patient tested genetically positive for celiac disease. The authors investigated autoimmune, neurological, psychiatric and oncological comorbidities at the end of the follow-up. They reported, as expected, ageing-associated comorbidities. However, their prevalence was not statistically different between the AGA positive versus AGA negative group, except for neurological diseases (p=0.017). These conditions included stroke, Alzheimer disease and polyneuropathies. If only new cases of neurological diseases, diagnosed during the follow-up are counted, the significance vanished. These data suggest that the elderly with AGA antibodies but with negative genetic tests for celiac disease have more neurological comorbidities than those with negative AGA suggesting that these neurological diseases were present at the baseline. We would like to know if in the patients with neurological disorders, the patients were also stratified according to specific pathologies, and if there were differences between AGA positive and AGA negative cases. It would be interesting to know if dementia or polyneuropathies or strokes are more frequent in one group than in the other, rather than in the neurological comorbidities taken together. On the other hand, we suggest that in a future approach, the authors will search for the role of the alteration of circadian rhythm in the elderly; this factor may influence their neurological and mental health [2, 3]. The same is true for some autoimmune conditions, some of which have been investigated in this study, which can also be influenced by the circadian rhythmicity [2, 4]. Another putative mechanism of the link between occurrence of neurological conditions and gut conditions is of course microbiota [5], which was not evaluated at the baseline in this population.

**Dinu Iuliu Dumitrascu[1], Aurel Popa Wagner[2,3]**
1) Dept. Morphological Sciences, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania; 2) Dept. Biochemistry University of Medicine and Pharmacy, Craiova, Romania; 3) Klinik für Psychiatrie, Neurologie, Psychosomatik und Psychotherapie im Kindes- und Jugendalter University of Rostock Germany

**Correspondence:** Dinu Iuliu Dumitrascu, d.dumitrascu@yahoo.com

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## Reply,

**To the Editor,**

We appreciate the comment by Dumitrascu DI and Popa-Wagner A [1] with regard to our paper [2]. We compared mortality and morbidity of persistently AGA-positive and AGA-negative subjects during a long-term follow-up of 12-13 years since the initial antibody analysis. We found cumulative prevalence of neurological diseases more frequent in the AGA-negative group in this register-based study. We had, however, clinically examined the whole AGA-negative group but only about one third of the AGA-positive group in our earlier study [3], which probably caused bias to our results. Most common

neurological diseases were stroke (17.2% in AGA-positive, 22% in AGA-negative group), Alzheimer's disease (in 4.9% and 14%), polyneuropathy (in 7.4% and 8%) and peripheral nerve or nerve root entrapment (in 5.7% and 10%, respectively). Differences in individual neurological diseases between the AGA-positive and the AGA-negative groups were analyzed and not statistically significant. We considered that at least no link between AGA-positivity and neurological diseases was proved in our study.

We also thank them for the comment concerning circadian rhythm and its influence in health. Interestingly, a recent study explored by a genome-wide transcriptomic analysis duodenal mucosa of non-coeliac gluten sensitivity -patients and found indication of a possible implication/dysregulation of circadian rhythm in non-coeliac gluten sensitivity [4]. Dumitrascu DI and Popa-Wagner A also underlined the possible role of gut microbiota in health and disease, especially neurological diseases. Changes in microbiota in gluten-related disorders coeliac disease, non-coeliac gluten sensitivity as well as irritable bowel syndrome have been reviewed recently [5]. The data especially on non-coeliac gluten sensitivity in still sparse. Unfortunately, we were not able to study these interesting and important issues in our earlier studies. Obviously, these matters are good subjects for further studies.

**Anitta Ruuskanen[1], Katri Kaukinen[2]**

1) Department of Neurology, Päijät-Häme Joint Authority for Health and Wellbeing; 2) Department of Internal Medicine, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

**Correspondence:** Anitta Ruuskanen, anitta.t.ruuskanen@phhyky.fi

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