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REVIEW

COVID-19 and the enteric system: rapidly propagating issues

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ABSTRACT

The newly described SARS-CoV-2 respiratory virus is now righteously presenting as an ominous threat, based on the speed with which it originated a zoonosis from bats; advancing at a similar rate, the virus has placed mankind before a pandemic, with an infection toll of some 431 million, and a lethality of 5,9 million (as of February 25, 2022). The size of the harm that this agent can unleash against us is appallingly wide, from brain ischemia to foot chilblain, passing by heart massive infarction. Designing a possible response, we reappraised the well-known equation depression-inflammation, and tested the hypothesis that an upgraded ease-of-mind might help reduce the host's hospitality towards SARS-CoV-2. With time passing, it becomes increasingly evident that the virus shall tend to progressively occupy spaces, replacing pandemics with an apparently calm endemicity. This will have to be avoided, and surveillance of society on psychological terms will be one tenet. Needless to say, the role of the enteric tract in these issues is growing higher, and it will be narrated to seal the matters with the last (not the least) touch of glue.

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Some 2 years after official initiation of combats, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is maintaining its traditionally noxious power (inflammation), and is implementing it through new pathways (variants).[1] As an example of one of the most affected states, with approximately 431,452,401 confirmed cases of COVID-19 (as at 25th February, 2022), Italy ranks 10th in the world ranking led by the USA with approximately 80 million.[2, 3] The infection alarm broke out abruptly February 2020 with notice of a cluster of infected cases expanding from a highly populated and industrialized area in the North;[4] it soon became clear that at that time mainland China had already been invaded and the virus was heading West.[5] Next, the infection tide swept the country, marked by a few never-seen-before episodes that reminded elderly people of the last World War,[6] and simply shocked to tears the remaining.[7] Amid all, the scenes of hundreds of deadly bodies taken to the graveyard on military trucks, hit the world crowds. Then, the story becomes today's chronicle. After a misleading sense of virus fading away in summer, the infection came back running in fall, making the lethality figures fly sky-high again, and prompting resort to two measures: lockdown and vaccination. Pandemics

and related mass confinement have been linked to increased rates of stress, anxiety, depression, and post-traumatic stress disorder, according to a growing body of research.[8-10] Although research on Coronavirus disease 2019 (COVID-19) is limited, there is increasing concern that the combination of COVID-19 outbreaks and the use of long-term stay-at-home orders would have a major impact on the communities affected. Indeed, the COVID-19 pandemic has posed unparalleled threats to the world's health, social, and economic structures.[11, 12] Due to several concerns, public education about COVID-19 vaccination is vital to the effectiveness of a national COVID-19 vaccination program. In contrast to other vaccines currently in use, the production of current vaccine candidates has been significantly accelerated. As a result, ongoing communication efforts would be expected to stress that no sacrifices in terms of safety or effectiveness were made. Similarly, since certain vaccines rely on novel technologies (such as mRNA), comprehensive and easily accessible information must be made available to the general public. These issues would also cause anti-vaccine feelings to grow, necessitating the development of effective communication strategies to address this issue.[13] Such two measures (lockdown and vaccination) need an extended discussion, and, in our opinion, are those that justify our tearing of the readers' time. In this narrative review we asked whether it is possible to interrupt this chain of automatic thinking by introducing novel concepts and metrics that best frame COVID-19 into psychologic/psychiatric arguments.

Lockdown and vaccine

The term lockdown indicates a measure that is well-known to all clinicians dealing with communicable diseases: a progressive segregation of the individual from social life (both leisure and work) to the very extreme step of total abolition of contacts, reinforced to attain the full-blown lockdown regime.[14] While the scope of these maneuvers is to abolish contagion and allow a flat spreading curve, this time lag of forced inactivity should be exploited to boost a vaccine campaign. Though this qualitatively corresponds to truth, several contradictory effects have emerged, forcing a balanced reappraisal of these policies.[15] Perhaps the full balance of the pros-and-cons of a regularly conducted lockdown has been presented with mixed accents depending on country legislation and agreements. At any rate, in roughly 15 months since its initial activation, for example in Italy, various problems have begun to appear and detract from the final balance, as following.

Interpersonal contact

Segregation is inducing several mainly negative psychological changes (depression, anxiety) among the segregated persons and their loved ones, beginning with the imposition that all interpersonal contact be mediated using a plastic sheath. On this line, little needs to be spent to account for the state of mind of millions of youngsters locked out of schools.[16] Finding yourself locked out of the school and locked in the traditional family house sounds for the youngster like the state's endorsement of the violent halt of (the yet rocky for most) journey from mom's and dad's protection to a responsible citizenship.[17] Many researchers as early as now fear the consequences of future welding between these psychologic wounds and the physical ones (often presenting with the worrying picture of an early atherosclerosis) exhibited by the newly defined category of the "Long Covid Haulers."[18] Multiple symptoms involving the lungs and other body districts may occur in patients with long-COVID.[19] Fatigue, exhaustion, joint pains, and low-grade fever; cough, shortness of breath, and chest pain; headaches, cognitive blunting ("brain fog"); rashes such as chilblain-like lesions (*e.g.*, "COVID toe") and vesicular or maculopapular rash; mental health problems such as mood swings; and thromboembolic disorders are just some in a crowded list. Waxing and waning as they can be, these signs/symptoms do float yet in a basin of unquenched inflammation, as emerging clinically with persistent symptoms of exhaustion. In addition to the psychological effects of lockdown, the unmatched levels of stress caused by COVID-19, ranging from fears about the future, job loss, expectation anxiety, and concern for, and death of, loved ones from the virus, have negatively impacted the mental health of many

people (living) over the last ten months. Furthermore, there is mounting evidence that infection with SARS-CoV-2 can result in long-term cognitive impairment. Even in people who were only slightly impaired during the acute infection, COVID-19 can cause long-term cognitive impairment. It is also unclear how long this will go on for.[20] Last but not least, a few psychiatrists are now realizing that home segregation may bring about two negative vectors. Physically, repeated re-infection may occur amid the ones supposed to be protected under the shared ceiling, with not even pets allowed to escape;[21] mentally, the house begins perhaps to be perceived as the safe shelter against an outer world that is daily more appalling, and less friendly.

SARS-CoV-2 vaccine

Early in the pandemic breakout, we searched the literature for any updated anti-viral algorithm. We came across the description of a series of synthetic nucleotides, generically named poly(I:C). Being artificial dsRNAs, they exhibited an array of structural and functional characteristics that here we just touch on schematically, as an extended discussion is dedicated to them elsewhere.[22] Poly(I:C) (available on the USA market as Hiltonol, Oncovir Inc., Washington, WA, USA) behave as activators of unprimed immunity channels primarily involving boost of the interferon (IFN) pathways, the main gate to antiviral control; its action is species-specific but is virus non-specific (the crucial pathway to the universal anti-virus power); this immunity gets enhanced in minutes after the signal released by the orchestrating cell, and is not halted by attacker-target genetic mismatch.[23] Of utmost importance, it is not hindered by any viral genome variant. The application of the inducer (Hiltonol or others) requires a nasopharyngeal patch. The curiosity of the science world for this algorithm grew rapidly after our initial notes, and the programs of non-specific immune stimulation, including the one using Hiltonol, were rapidly reunited under the umbrella term "Trained immunity,"[24, 25] listing now beyond Hiltonol, a number of stimulator antigens, including even the tuberculin extract Bacillus Calmette-Guérin (BCG), each and all capable to activate systems of yet loosely linked effectors. The bottom line is the achievement of satisfactory control of various pathogens, for the moment leaving aside the twisting ways of T-cell mediated (acquired) immunity.[26] Long overdue, a regular COVID-19 vaccine program has recently been initiated, based on the availability of the Astra-Zeneca, Pfizer, Johnson & Johnson, and Moderna preparations.[27-29] Unfortunate, but somewhat expected, a number of accidents are now making the vaccine stairway a bit rocky.[30-32] We shall turn to this point only when useful to support the discussion. In conventional immunization designs, huge crowds of candidates are requested to gather together, generally in public areas, to allow professional crews to stick the vaccinating needle into hundreds of deltoids in a matter of hours. Gentle, bright, and well-organized or presented as they can be, such huge operations might always (duly) meet with the disappointment (anxiety) of a few, who had converged to that promising meeting site as though they were the addressee of a heavenly miracle to dissolve their sufferings at once: duly informative dialogue with a reliable authority, if missed beforehand for any reason, is no longer allowed in that noisy location. Such disappointment in our opinion might be favored by unduly long periods of ill-justified lockdown. The wounds of this misunderstanding may even convince a few to withdraw their consent.[33, 34] In our opinion, a solution to these difficulties is inherent in trained immunity algorithms, as detailed: 1) the administration of the pharyngeal patch in relaxed silence might recall a religious ceremony to some people; 2) in average, treated people are expected to enjoy a period of 3 months in a condition of viral resistance;[23] 3) those lucky in these crowds, (bearing the leader's signatures), are expected to rapidly organize meetings among workmates, to establish work shift schedules, adapting to the alternating periods of viral resistance (see point 2 above) – in any case, people are expected to feel as though they were born again, free to use their voice and breath, magically disappeared under a kind of malignant spell: in a word, they may return master of their actions; 4) worth to meditate, SARS-CoV-2 has smartly developed a heightened adaptation to be conveyed by lung droplets – thus, control of virus spread does cost aboli-

tion of language communication, and, perhaps less immediate to realize, prohibition of music played by wind instruments, a childish memory for most, an untold life pivot for more than we might suspect;[35] and 5) in a few, perhaps surprising words, trained immunity against COVID-19 might restore adult duties, and childish joy, both crucial for mental sanity (rather a rare circumstance for a vaccine, these points represent added values, that nothing have to do with strict virologic issues). By contrast, a couple of most recent papers has considered these issues under a major sociologic perspective. The reappraisal is started out by blaming the policy to concentrate the major effort on the detection and treatment of COVID-19, a policy that has left obviously underfunded the problem of non-communicable chronic disease (NCDs).[36] As a matter of fact, the Authors emphasize that in recent years NCDs have steadily increased their prevalence (not only in the Western World) and nowadays their societal impact recalls that of COVID-19;[37] the obvious argument on the lacking demonstration of a communicable agent in NCDs, in currently published papers, can be answered by observing that NCDs do recognize their communicable factor in a vast number of upstream barely recognized factors: urban design, housing, poverty: last but not at all least, availability of junk food and alcohol, both encouraging epidemics of (concealed) NCDs. Thus, COVID-19 seems to rely on an obvious communicable agent, NCDs by contrast, might depend on indolently creeping social factors.[38] This mental construct interestingly sees potential NCDs- facilitating- factors as prion-like proteins:[39] one of them, inserted into a line of normal proteins, can mismatch them, disturbing a balance required for health. In a real-life example: negative trends such as obesity and poor culture, may easily become tenacious in invading a well-off neighboring community in chase of easy money.[40] Such interplays may be anticipated to worsen in the artificial atmosphere of urbanized areas, where individuals living closely are mostly keen at an interaction, whether good or bad. In urbanized areas structures were meant to ease individual and collective life. But in the case of a social crisis, obvious events such as public transport strike, or unexpected bank service shutdown, may affect the individual much more heavily than in simple rural communities.[41, 42] In the wishful thinking of most, modern society has been preemptively ruled to enhance crowd co-habitation; however, when the pivots jam up or crumble, the individual finds himself paying the heaviest toll. A few years ago, we and others, placed some commitment on profiling the many individuals who had had the privilege but also the challenge of confronting their life with the rapidly changing tides following World War II, wherein, chasing continuously after a new target, have often remained on the back-foot. These people, who seem very close to the category of NCDs, were named "inflammacitizens"[43, 44] by us and our colleagues, emphasizing the co-existence of depression/anxiety with chronic dys-immunity, a concept that nowadays most investigators are ready to share. Of course, immunopathology and close psychiatric counseling are most indicated for these post-industrial people. To this end, many contemporary experts would hold that COVID-19 can expose with the same ease biological, cultural, social, and digital faces.[45]

Pathologic notes

In the face of this evidence, neurologic changes induced by physical COVID-19 infection could easily be anticipated, and data[46] are now consistently holding that SARS-CoV-2 can directly trespass gut lining cells thanks to their membrane expression of the spec receptor Angiotensin-converting enzyme 2 (ACE2). Occupied by its regular ligand, the ACE receptor class constitutively exerts its inflammatory down-regulatory function, which in turn becomes lost when SARS-CoV-2 occupies the receptor and the link with the interleukin (IL)-6 pro-inflammatory cytokine gets lost with supervening inflammation. If intestinal symptoms can duly be expected to derive from the gut phase of SARS-CoV-2 infection, neurologic signs[47] can follow as easily the infection of the Enteric Nervous System (ENS). Creeping cranially on the path of the vagus, SARS-CoV-2 can reach higher brain stem structures. Either following ischemic inflammatory, or subtle neurologic networks, dispersing

symptoms along processes of variable length.[20] Production of reactive pathologic proteins with prion functions (alpha-synuclein)[48] do characterize these phases which share much in common with Parkinson's pathways.

Clinical notes

Reappraising the above data, in functional gastro-intestinal diseases, although numerous etiopathogenetic factors are involved (microbiome, low levels of inflammation, genetic predisposition, and others), the brain-intestine axis plays a fundamental role.[49] The stress resulting from the fear of becoming infected or from getting sick with COVID-19, more than 1 year of social isolation and a net reduction in physical activity has obviously also had an impact on functional gastrointestinal disorders. In a recent study,[50] in 13.6% of patients an important worsening of symptoms compared to the interval before the COVID-19 outbreak was found. Conversely, more than one third (36,4%) of patients declared their symptoms improved or extremely improved. One potential reason is that copying, and tension related to social activity and social interactions at work may be more bothersome for many patients with functional gastrointestinal disorders than being "locked" at home. Similarly, consuming a Mediterranean diet at home or, at least, having a more regular meals, while having fast and qualitatively unhealthy meals at work, may have had a positive impact on upper gastrointestinal symptoms. Furthermore, for patients suffering from irritable bowel syndrome with diarrhea, being able to always have their own bathroom available in case of urgency, may have decreased their related anxiety. In contrast, in the study, higher anxiety levels were found associated with the risk of worsening chest pain, epigastric burning, and abdominal pain.

Conclusions

The cases of post-COVID-19 syndrome, distinguished based on persistent neuro/psychiatric symptoms without obvious neuropathology, will need separation from organic central nervous system damage, wherein we already know that ischemic pathology is playing only a part of the drama.[51] The drawing our attention towards the long-Covid issue, inevitably can take to reappraising neuro COVID-19 with its innumerous pathways. Clinically, merging of COVID-19 and NCDs may tend to make a solid undifferentiated iceberg, that, just as an iceberg, can wander randomly, and hit and ruin any target in the unaffected society. Unequal opportunities to traditional life goals often mark such stormy phases in history, and punctual psychological help will make a crucial compass to minimize a social clash that many of us fear as one of an unprecedented severity.

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