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Trisomy 21 and the coronavirus disease 2019 (COVID-19): seven reasons to worry for a disaster

Dear editor.

We read the manuscript of Francisco Cammarata-Scalisi et al. with interest.[1] We agree the population with trisomy 21 should be considered at risk for coronavirus disease 2019 (COVID-19). Despite the current lack of data about SARS-CoV-2 and COVID-19 in patients with Down syndrome (DS), we believe there are seven reasons to worry for a disaster caused by COVID-19 in these patients:

First, as mentioned by Cammarata-Scalisi et al.,[1] DS patients more frequently develop severe respiratory symptoms because of respiratory anomalies, generalized hypotonia, cardiovascular disease and swallowing problems. In addition, these subjects often have altered immunity, which makes them more prone for infections.

Secondly, people with DS might be at risk to develop more severe forms of COVID-19 because of immune dysregulation and chronic auto-inflammation on molecular and cellular levels. People with DS might be more prone to develop severe cytokine release syndrome, which is thought to be an important factor in poor outcome in patients with COVID-19.[2]

In addition, as a third factor, we have our own hypothesis that cell entry for SARS-CoV-2 might be facilitated in patients with DS.[3] Different studies have looked at the role of the ACE-2-receptor, but the transmembrane serine protease TMPRSS2 (which works in close contact with this receptor) might be important too. TMPRSS2 plays a role in the proteolytic activation of the influenza virus and other coronaviruses, suggesting its possible role in SARS-CoV-2 cell entry. There's no evidence yet for the role of this protease in COVID-19, but it's modulation by sex steroids could also be part of the explanation for male predominancy in COVID-19. The gene for TMPRSS2 is located on chromosome 21, making DS patients possibly more vulnerable for a severe course of COVID-19.

Forth, as also mentioned by Cammarata-Scalisi et al.,[1] these patients have a poorer response to primary vaccination. Because of their altered immune response, DS patients may respond less to a potential vaccine against COVID-19 or may need an altered vaccination protocol. This vulnerability should be taken into account when vaccination campaigns are being rolled out.

A fifth reason to worry is the higher prevalence of comorbidities in DS patients compared to the general population. The prevalence of diabetes mellitus, congenital heart disease, obesity… is higher in DS patients when compared to the general population in the same age group. These comorbidities are independent risk factors for a more severe course and higher mortality of COVID-19.[4]

A sixth reason to worry comes with the fact that people with trisomy 21 stay more often in residential facilities. This comes with extra challenges. We've already seen long term care facilities are at higher risk for outbreaks of COVID-19, with often big clusters of infected people. Staff should be cautious not to be a vector of infection between residents, by applying social distance when possible, correct use of PPE and education to residents. Visitors should be screened for symptoms to prevent being an index for outbreaks in the institutions.

Finally, besides their medical status, people with DS often have more difficulties with understanding and complying with prevention rules for COVID-19 rolled out by the local authorities. A survey in a Belgian residential facility showed that patients with trisomy 21, but other residents as well, didn't fully understand the concept of social distancing or didn't apply to the rules.[5] They still looked out for physical contact with one another and didn't keep the imposed social distance when having contact with other people. This might put them at higher risk when having contact with a possible infected person. The same survey showed that mental health in residential facilities was at stake too. A lot of preventive measures were proclaimed in facilities to prevent residents. This resulted in less family visits, less group activities and a reduction in therapy sessions in patients who might already be more sensitive for changes in routine and behavior. We should be cautious for protecting these patients for a possible infection, but should likewise be aware that a lockdown and protective measures could cause collateral damage on their well-being.

It will always be difficult to balance between infection control on the one hand and social acceptability on the other hand. This can best be assessed at the local level, as opposed to adhere to comprehensive national guidelines that do not take into account the needs and weaknesses/strengths of specific target groups, e.g. our DS patients.

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Response to Editor's Letter: Trisomy 21 and the coronavirus disease 2019 (COVID-19): seven reasons to worry for a disaster

Dear editor:

We receive with great pleasure the Letter to the Editor from Rodiers & De Cauwer regarding our publication entitled: *Trisomy 21 and the coronavirus disease 2019 (COVID-19)*,[1] published in your prestigious Journal. Before making the comments, I wish to express that this article was the product of the inspiration originated by a patient who on social networks expressed the care we must have with the population with trisomy 21. From there arose the idea and need to express the conditions specific to individuals with this genetic entity at the beginning of the pandemic. We also appreciate the response to our article, as it expands and reinforces the importance of protecting the population with trisomy 21, in times when the information is continuous and relevant.

Two aspects previously mentioned were highlighted and include the greater frequency of developing chronic respiratory symptoms associated with respiratory anomalies, congenital heart disease, generalized hypotonia and alterations in feeding that can predispose to recurrent respiratory infections, all this coupled with various defects in the immune system that can aggravate its evolution and therefore have a worse prognosis.[1,2] On the other hand, individuals with trisomy 21 have a poor response to primary immunization and require a personalized vaccination protocol,[1] even with a possible vaccine against COVID-19, which should be taken into account in future vaccination campaigns.[1,3]

As Rodiers & De Cauwer well highlight,[4] among other causes that can influence a more serious presentation of COVID-19 infection in individuals carrying this genetic entity are the afore mentioned immunological dysregulation and chronic autoinflammation at the molecular and cellular level, which may predispose to developing a severe cytokine release syndrome.[5] These authors also hypothesize that COVID-19 cell entry may be facilitated in people with trisomy 21.[4] Likewise, the role of the ACE-2 receptor and transmembrane serine protease 2 that play an important role in proteolytic activation of the virus.[4,6] Although evidence is not yet confirmed, it could explain the predominance of the male sex in those affected and that the *ACE2* gene is located on chromosome X and *TMPRSS2* gene is located on chromosome 21 is highly relevant.[4]

However, the presence of obesity and diabetes mellitus, among others, may be higher in individuals with trisomy 21 than their peers without the entity, comorbidities that may constitute a risk factor for poor prognosis.[3,7] Additionally, as was commented by Rodiers & De Cauwer, the personnel who work in residential facilities and visitors must be careful not to be a vector of infection, along with following the regulations to avoid contagion and outbreaks in said institutions.[4] As highlighted by a group of researchers, in a study carried out in a residential center in Belgium, it showed that patients with trisomy 21, but also other residents, did not fully understand the concept of social distancing or such protection rules were not applied.[8] Another aspect that this study showed is the commitment of mental health in the individuals residing in these institutions before the protection measures, highlighting the decrease in visits from their relatives, as well as group activities and therapies, in search of a balance in that changes in routine do not affect and may cause collateral damage to their well-being.[4] Some tools such as

video calls with family members and therapies through audiovisual means can favor adaptation to new circumstances. On the other hand, the family group must implement similar prevention measures in the homes where an individual with trisomy 21 lives.[1]

In addition to the clinical conditions already described, these individuals may have difficulty in understanding and complying with the norms for the prevention of infection with COVID-19, corroborating the aforementioned. For the aforementioned, it is necessary to find a balance between the prevention of infection and that these actions do not alter the integral development of individuals with trisomy 21.[4] Although complex, we must try that these experiences generate learning in order to support this population and even others in similar circumstances.

This exchange could be the beginning of creating an international support group for individuals with trisomy 21, where any researcher or group from any part of the world who has the desire to collaborate and share their experiences or wishes to make any contribution to the research as any contribution to the research is welcomed.

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