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Haemophagocytic lymphohistiocytosis in COVID-19 cases?

OPINIONS

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Could haemophagocytic lymphohistiocytosis be a factor in severe coronavirus disease?

Puja Mehta and colleagues have recently published an article in The Lancet in which they discuss whether secondary haemophagocytic lymphohistiocytosis (HLH) can be triggered by coronavirus (1). The Journal of the Norwegian Medical Association wished us to comment on this topical issue. Infections are one of several causal triggers for this severe hyperinflammatory condition, and viral infections, including SARS, are assumed to be the causal factor in 6–28 % of patients with this diagnosis (2–5).

Observations point to the importance of treating haemophagocytic lymphohistiocytosis with immunomodulating drugs. In a study of patients with this condition, the causal trigger for which was Epstein-Barr virus infection, it was found that mortality was 14 times higher in the group that did not receive this kind of treatment (4). However, no such results have been found for other viral infections. It should be noted that no randomised controlled trials of treatment regimens for HLH have been undertaken (3).

COVID-19 (*coronavirus disease 2019*), caused by SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*), is now spreading as a pandemic. Most people will not become seriously ill, but among those needing intensive care treatment in hospital, the mortality rate is high. Massive lung affection and development of acute respiratory distress syndrome (ARDS) are characteristic of these patients. In many cases, severe systemic and local inflammation can also be observed, which may exacerbate the condition. The background for the phenomenon has not been identified, but it has been shown that SARS-CoV-2 can activate inflammasomes in the innate immune defence system, with the release of interleukin-1, by binding to angiotensin-converting enzyme 2 in the lung tissue (6). A massive release of interleukin-6 is also seen in cases of COVID-19. It is not inconceivable that a 'cytokine storm' of this type could lead to the development of secondary haemophagocytic lymphohistiocytosis with cytopenias, significant haemophagocytosis in bone marrow, and low fibrinogen concentration. High ferritin levels and persistently high CRP can give rise to suspicion that a cytokine storm forms part of the clinical picture.

COVID-19 is a new condition, and although several forms of treatment are being tested in randomised trials, there is currently no established drug treatment. Trials of interleukin-6-blockade with tocilizumab are being considered in cases of acute respiratory distress syndrome associated with COVID-19, and interleukin-1-blockade with anakinra is also being discussed. It

is nevertheless too early to draw any conclusions about whether these drugs work. If a hyperinflammatory condition similar to HLH is suspected in COVID-19 patients, specific treatment of this condition could be considered. This should in such cases be undertaken in the form of randomised clinical trials, which the World Health Organization recommends for all new, experimental therapy to combat this global disease (7).

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