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LEADING TOPIC

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# Incidence of dystonia related to COVID-19 infection

Marita F. Thiel, Wolfgang H. Jost

Parkinson-Klinik Ortenau, Wolfach, Germany

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## To the Editors

In December 2019 cases of infection caused by the new coronavirus SARS-CoV-2 were reported for the first time in the Chinese city of Wuhan. The virus spread at an immense speed, first in China, then worldwide. By March 2020 there was a global pandemic, which was confirmed by the World Health Organisation (WHO). According to the data of the WHO, there had been 663,640,386 confirmed cases of COVID-19, including 6,713,093 deaths, reported to the WHO up until January 2023. In the description of clinical manifestations, the respiratory system was the initial concern. However, the symptoms of headache and fatigue soon shifted the focus towards neurological involvement [1]. Neurological symptoms such as loss of smell and taste, CNS-related cerebrovascular events, strokes, epilepsy, and encephalopathies were reported, as were pathologies affecting the peripheral nervous system such as muscular pain [2]. Furthermore, cognitive impairment and autoimmune-associated pathologies such as Guillain-Barré syndrome and vasculitis has also been described [3]. In 2020, Paniz-Mondolfi et al. detected the virus in neural and endothelial cells in the frontal brain of a patient who had died from SARS-CoV2 infection [4]. For the route into the brain, different pathways are conceivable. These include the retrograde route via the olfactory nerve or a disrupted blood-brain barrier through leukocyte migrates [5]. The pathophysiological correlation can possibly be explained by the binding of the viral spike protein to angiotensin converting enzyme 2 (ACE2), which is expressed in many tissues, as well as in the brain [6]. In addition to that, autoimmune processes possibly triggered by T-cell involvement or the virus itself are being considered [7].

We performed a literature search in the PubMed database focused on the period from the outbreak of the infection in December 2019 until January 2023. We only considered articles in English. The filters applied included books and documents, clinical trials, meta-analyses, randomised controlled trials, reviews, systematic reviews, and case reports. We did not consider articles with a paediatric background. We also disregarded an association with pregnancy, vaccination, or therapeutic procedures in the context of infection.

We also looked to see if there were any cases reported to our dystonia outpatient clinic that were suspected to be related to COVID-19 infection, or if there was evidence of increased prevalence.

We began the literature search by using the keywords 'COVID-19', 'SARS-CoV-2' and 'neurological symptoms'. The term 'symptoms' was synonymous with 'complications' and 'manifestations'. This keyword search yielded 1,423 hits. We reviewed the individual titles. In case of unclear relevance, we additionally evaluated the respective abstracts, and full texts if available. Eventually we found 261 publications that had been published since the outbreak of the infection until the beginning of January 2023 and that dealt with the relationship between SARS-CoV-2 and neurological symptoms. The vast majority of these were reviews and systematic reviews. A wide range of neurological symptoms were described in this literature, but dystonia was not among them. A narrowed search using the keywords 'SARS-CoV-2 and dystonia' yielded four hits. Of these, two articles were not relevant to the topic and a third addressed the issue of worsening movement disorders that already existed before infection. In their review, Brandão et al. addressed the issue of movement disorders that occurred in the setting of SARS-CoV-2 infection. Based on

**Address for correspondence:** Marita Thiel, Parkinson-Klinik Ortenau, Kreuzbergstr. 12–16, 77709 Wolfach, Germany; e-mail: m.thiel@parkinson-klinik.de

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their literature search of 200 articles, they found 44 articles in which movement disorders were mentioned. From these, they extracted 93 patient cases in which a movement disorder had newly occurred during a SARS-CoV-2 infection. Dystonia was documented in just one case [8]. This case was based on the analyses of Franke et al. Using blood and cerebrospinal fluid samples, they had investigated possible autoimmune processes associated with SARS-CoV-2 infection. Their studies were based on data from 11 critically ill patients receiving intensive care. For one patient they described upper extremity dystonia. This was a 78-year-old male with a PCR-confirmed SARS-CoV-2 infection. Delirium was coexistent [9]. No further search results were found.

Since the epidemic of encephalitis lethargica 100 years ago, medicine has been aware of the possibility of extrapyramidal motor disorders due to infection [10]. The association of dystonia and encephalitis in general has been described and discussed several times already [11, 12]. Since the neurological symptoms of SARS-CoV-2 infection include encephalitis, we expanded our literature search to include the keywords 'encephalitis' and 'SARS-CoV-2'. This yielded 245 hits. 10 of these articles focused specifically on the above-mentioned topic. Based on the abstracts and the available full texts, we found no evidence for a description of dystonia occurring under SARS-CoV-2-associated encephalitis.

In our view, another aspect arose from the frequently described association of autoimmune-triggered diseases and dystonia [13]. COVID-19 is also seen as a possible trigger of autoimmune processes in the context of infection [14, 15]. For these keywords, the literature search yielded 760 hits, 93 of which were related to the above-mentioned context. They dealt with possible autoimmune processes related to all organ systems. Dystonia among autoimmune-triggered diseases caused by COVID-19 was found in the literature.

We have not had more enrollments in our dystonia outpatient clinic than in previous years, nor have we seen any cases where a correlation might be suspected.

Infection with COVID-19 may be associated with a variety of concomitant neurological symptoms in addition with respiratory system involvement. Our literature search revealed evidence of one case in which dystonia had occurred secondary to infection. This was a 78-year-old male patient with a severe course requiring intensive care. His dystonia was described for the upper extremities with right-sided emphasis. Delirium was coexistent [9]. Whether the rare mention of new-onset dystonia in our literature search (n = 1) equates to a low incidence of dystonia among SARS-CoV-2 infection cannot be adequately assessed based on the current data. The conclusion that dystonia is a rather rare symptom might be obvious but cannot be considered conclusive. In the case of dystonia, the cause could lie in the distant past. It might be necessary to reexamine the question of how frequently it actually occurs in the course of the disease.

Further analyses and studies are needed to determine whether dystonia, although extremely rare, is one of the neurological symptoms of COVID-19 infection, or whether the result of our literature search is a mere chance finding with no relevance. Therefore, physicians should be sensitive to the early course of the infection and also to its long-term course

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