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Contents

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LETTER TO THE EDITOR

Impact of COVID-19 pandemic on the neuropsychiatric status of Wilson's disease

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Abstract

We have read with interest the Letter to the Editor by Drs. Zhuang and Zhong, who presented the clinical data of 68 patients with Wilson's disease (WD) who were admitted to the hospital before and during the coronavirus disease 2019 (COVID-19) pandemic, and appreciated their findings on hepatic and some extrahepatic manifestations. Nevertheless, given the strong impact of the pandemic on patients with neurological and psychiatric disorders, we would have expected a worsening of the psychiatric and/or neurological impairments in these patients. In contrast, according to the authors, these manifestations remained, somewhat unexpectedly, unchanged. This finding is in contrast with most of the current literature that highlights not only an increased incidence of mental health disorders in the general population but also an exacerbation of neurological and psychiatric symptoms in patients with chronic diseases, especially in those with pre-existing neuropsychiatric disorders, such as WD. Although the study was mainly focused on the hepatic features of WD patients taking anti-copper treatment, a generic and cumulative definition of neurological and psychiatric manifestations, as in this study, does not allow for further considerations. Future studies during and after the pandemic are necessary to clarify the real impact, either direct or indirect, of the COVID-19 pandemic on the neurological and psychiatric symptoms of WD patients.

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Core Tip: In the interesting letter by Drs. Zhuang and Zhong, the psychiatric and neurological manifestations of 68 patients with Wilson's disease who were treated with anti-copper therapy unexpectedly remained unchanged after the pandemic. Given the impact of the pandemic on patients with neurological and psychiatric disorders, a worsening in the severity or frequency of these manifestations could have been expected. The possible reasons underlying this finding, including the relatively small sample size, the effect of therapy, and the patients' resilience, are discussed.

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TO THE EDITOR

We have read with interest the Letter to the Editor by Zhuang and Zhong[1], who presented the clinical data of 68 patients with Wilson's disease (WD) who were admitted to the hospital before and during the coronavirus disease 2019 (COVID-19) pandemic in Guangzhou (China). Of note, none of the patients had COVID-19. As WD is a rare chronic systemic disease, the impact of the pandemic on the multiorgan clinical status of these patients is still unclear and, therefore, certainly worth investigating. Indeed, we have appreciated the findings that showed a marked shortage of medical resources for the clinical management of patients with WD during the pandemic, as well as the findings that patients who consistently took anti-copper medications showed no significant difference in hepatic and some extrahepatic features, although the incidence of their complications (especially those related to infections) significantly increased. For these reasons, we fully support the authors' recommendations to strictly adhere to the anti-copper therapy and closely monitor these patients to prevent complications[1].

However, given the strong psychological and socio-behavioral impacts of the pandemic on the clinical symptoms of different neuropsychiatric disorders[2,3], a worsening, or at least an increase in the frequency or severity, of psychiatric and/or neurological manifestations in WD patients could have been expected. Conversely, according to the authors, before the COVID-19 pandemic, 50 out of the 68 patients had neurological involvement, and three had psychiatric manifestations, which remained, somewhat unexpectedly, unchanged after the pandemic (49 and 4 out of the 68 patients, respectively)[1]. Although this study was mainly focused on the hepatic features of WD, only a generic and cumulative definition of neurological and psychiatric manifestations was adopted without additional specifications (*e.g.*, type, onset, severity, and duration), which did not allow for any further considerations; indeed, these apparently negative results were not discussed. Moreover, it was not specified how neurological and psychiatric manifestations were evaluated (*e.g.*, were specific scales used?), both at the study entry and at the end of the study. A more detailed stratification, for instance, by type of manifestation (such as cognitive or motor deficits, among the neurological aspects, and anxiety or mood disorders, among the psychiatric conditions), would have likely disclosed additional findings.

In this context, COVID-19, being the major infectious outbreak in the 21st century, has led to an unprecedented global hazard to mental health. A recent systematic review[4] on the impact of the pandemic on mental health in the general population found significantly higher rates of symptoms of anxiety (6.3%-50.9%), depression (14.6%-48.3%), post-traumatic stress disorder (7.0%-53.8%), psychological distress (34.4%-38.0%), and stress in general (8.1%-81.9%) in several countries worldwide, including China. Although a certain degree of heterogeneity was noted across the studies, the risk factors associated with these manifestations included, among others, a

younger age (≤ 40 years) and comorbid chronic or neuropsychiatric illnesses[4], such as WD.

On the other hand, the negative effect of the COVID-19 outbreak on mental health and health care services has been and will likely continue to be significant because of the unpredictability and uncertainty of the pandemic, the associated lockdowns, physical distancing, and other containment strategies, and the resulting economic breakdown[5]. Reasonably, as also observed in the Letter discussed here[1], the impact of the COVID-19 pandemic on the utilization of health care services, in terms of outpatient visits, hospital admissions, diagnostic exams, and therapeutic interventions, decreased by approximately one-third during the pandemic, with considerable variations and greater reductions among people with less severe illness[6]. Throughout the pandemic and even still, there has also been evidence of increased levels of relapse, in people with pre-existing mental health conditions and even in people with no previous history of a mental health disorder[7]. In particular, patients with pre-existing anxiety, depression, panic, delirium, psychosis, and suicidality appear to be extremely vulnerable[8].

Nevertheless, the matter is still debated, since it has also been observed that some individuals with severe mental illnesses, such as schizophrenia and affective disorders, may not report a worsening of symptoms, thus appearing to be resilient to the negative effects of the pandemic[9]. However, frequent assessments and periodic follow-up are needed to determine whether this resilience will persist as the pandemic progresses or after its end. In this context, in addition to the relatively small sample size, the potential effect of anti-copper therapy in this cohort, and the fact that none of the patients were affected by COVID-19, the patients' resilience might also represent a possible reason that supports the findings reported by Zhuang and Zhong[1]. However, their patients did not seem to be affected by severe psychopathologies, thus making this possibility less likely to justify the authors' conclusions. Moreover, although WD is a rare pathology, it is worth mentioning some methodological issues in the study[1] that may be appropriate and relevant for discussion. In particular, the relatively small sample size, the fact that not all patients were admitted to the hospital during the pandemic, and the possibility of the patients' resilience raise crucial questions that need to be addressed in the near future. Further multicenter prospective cohort studies, retrospective studies, and case-control studies on inpatients and outpatients with WD, both before and after anti-copper treatment, should be performed.

Less is known about the effects of the COVID-19 pandemic on neurological disorders, although a recent systematic review concluded that patients with pre-existing conditions (including those characterized by cognitive impairments or parkinsonism, which may be part of the clinical spectrum of WD) can develop exacerbation of their neurological symptoms, thus encouraging clinicians to be aware of this risk and to focus on its prevention and early management[10]. In this context, it is known that concomitant infections, especially infections of the respiratory and urinary tracts (such as those reported in the letter[1]), frequently worsen the symptoms and the course of several neurological diseases, including parkinsonism and dementia[11,12]. Therefore, the fact that the increased infection incidence detected in the study[1] did not induce an even transient worsening of the patients' clinical status remains to be explained or at least briefly commented on.

In conclusion, the study by Zhuang and Zhong[1] provides a valid clinical basis for the proper management of WD patients during the pandemic, thus representing an advance in this field of clinical and research interest. However, further independent multicenter studies during and after the pandemic are necessary to clarify the real impact, either direct (*i.e.*, infected patients) or indirect (*i.e.*, psychological and sociobehavioral consequences), of the COVID-19 pandemic on the neurological and psychiatric symptoms of WD.

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