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COVID-19

Two cases of Huntington's disease unmasked by the COVID-19 pandemic

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Introduction

Movement disorders of new-onset are increasingly being described in patients with SARS-CoV-2 infection [1]. Imaging and cerebrospinal fluid (CSF) studies in such patients suggest a possible underlying post-viral immune mechanism, ruling out structural brain lesions and encephalitic processes [1]. Interestingly, SARS-CoV-2 infection appears to be able to affect several crucial cellular pathways, which are also relevant in cellular aging and in neurodegenerative diseases [2]. These include immune activation and inflammation. Of note, both these responses are induced following immunization with effective vaccines, which are enhanced in patients who previously recovered from COVID-19 [3]. As the pandemic continues, increasing evidence has drawn attention to the indirect and systemic effects of the virus, which could be an environmental modifier in patients genetically predisposed to develop Huntington's disease (HD).

Methods

Here, we report on two patients who manifested the first symptoms of Huntington's disease (HD) following either COVID-19 infection and vaccination, respectively. Patient 1 started to experience involuntary movements involving hands during the mild acute phase of COVID-19 (see Supplementary Materials for the full case description). His clinical examination revealed choreiform movements of both hands and feet without other focal neurological disturbances (Supplementary Video 1). Patient 2 presented with generalized involuntary movements a few days after getting the first dose of the BNT162b2 vaccine (Pfizer–BioNTech) mRNA vaccine (see Supplementary File 1 for the detailed description). Six months before this presentation, she had a mild COVID-19 infection. On examination, she had widespread choreiform movements, motor impersistence, slight hypotonia, and inability to tandem walk (Supplementary Video 2).

Genetic testing revealed 33 cytosine-adenine-guanine (CAG) repeats on one huntingtin allele and 15 on the other allele in patient 1, and 40 CAG repeats on one allele and 21 on the other allele in patient 2. An extensive work-up for other acquired and genetic causes of chorea was negative in both cases (see Supplementary file 1). Their family history was otherwise negative. Real-time reverse transcription PCR assay of the CSF sample was negative for SARS-CoV-2 in patient 1.

Discussion

HD is an autosomal dominant neurodegenerative disorder characterized by involuntary movements, psychiatric disturbances, and cognitive decline. HD results from an expanded CAG repeat in the huntingtin gene and predominantly affects striatal medium-sized spiny neurons, with prominent atrophy in the caudate and putamen. Affected individuals typically begin to show motor signs around 40 years, but with substantial variability in the clinical presentation and age of onset, even across carriers of the same-sized expansion [4]. Repeat CAG lengths ≥ 40 are associated with nearly full penetrance by age 65 years, but variable age-dependent penetrance has been reported between 36 and 39 CAG repeats [4]. CAGs less than 36 are usually non-pathogenic, but have the potential for germline expansion into the HD range. The size of the CAG expansion is the most critical determinant of age at clinical onset, accounting for between 47 and 72%

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of the variance in different HD populations [4]. In addition, genes other than the HD gene and environmental factors may influence the age of onset of the disease [5].

The variability in onset age is particularly evident in carriers of the reduced penetrance allele (36–39), for whom environmental components could be playing a major role, and even in individuals with intermediate alleles (27–35) [5].

Several studies investigated the capability of SARS-CoV-2 to directly invade and damage neurons and to reappear later with neurological diseases, like herpes simplex virus, but with a lack of evidence for productive infection of the CNS parenchyma [2]. Accordingly, anatomopathological findings suggest that the neuronal damage and loss are unlikely to be caused by a viral infection of brain tissue [2]. Furthermore, a direct viral neuroinvasion in the brain is not supported by CSF findings in the literature and in patient 1 of our study, who tested negative for CSF Sars-COV-2 mRNA detection. Differently, para-infectious/post-infectious immune-mediated mechanisms induced by systemic SARS-CoV-2 infection appear to be a predominant pathogenic mechanism of neurological involvement [2].

It is plausible that systemic inflammatory effects and altered immune responses induced by SARS-CoV-2 disrupt the blood–brain barrier integrity and exert a negative impact on cerebral homeostasis and function, favoring neuronal degeneration in susceptible patients [2]. Notably, long-lasting inflammatory processes have been shown to develop within the CNS after several viral infections and might trigger or accelerate subclinical mechanisms that underlie an earlier onset of neurodegenerative disorders in individuals already at risk [2]. Nonetheless, neuroinflammation is one hallmark of HD [6], mediated through the cytokine expression and the activation of microglia and astrocytes in the striatum and cortex which have been correlated both with the pathology and severity of HD and are already evident in presymptomatic HD mutation carriers [7]. Interestingly, it should be further noted that viral infections have already been implicated as potential environmental factors in some cases of HD, causing an earlier onset compared with subjects without concomitant infection [8]. In patient 1, after a thorough study and the exclusion of HD-like disorders, the appearance of the mild choreic syndrome after COVID-19 infection led to hypothesize that CAG 33 repeats could be an essential predisposing factor for developing HD-like symptoms.

Likewise, looking at patient 2, we may speculate that an enhanced specific immune response post-vaccination in a history of previous COVID-19 infection may act as a trigger of clinical disease expression in at-risk individuals who already have an underlying disease process and are on the cusp of manifesting the disease [2, 3]. Moreover, mRNA vaccines are known to induce a highly effective humoral and cellular immune response [3]. Immune activation has also been demonstrated in the peripheral blood of HD subjects, likely reflecting the processes observed in the CNS [6]. However, in HD, it is still unclear whether immune-mediated neuroinflammation is a reactive process or has a detrimental effect on disease progression [6].

While being the carrier of 40 CAG is certainly a predisposing factor to develop HD, the role of the enhanced immune-mediated neuroinflammation induced by the vaccine (in a patient with a prior natural infection) in accelerating an underlying neurodegenerative process will require more evidence, leaving open the question that the onset of chorea in this clinical case could still be a coincidental association. In this view, the temporal association between symptom onset and vaccination might just indicate a nonspecific immunological mechanism of bystander activation.

In addition, a causal connection to the SARS-CoV-2 pandemic in these patients cannot be drawn, and the lack of neuropathologic assessment and follow-up data represent major limitations of our report. However, while in case 2, the vaccination could have merged with the diagnostic phase of HD in a patient with fully penetrant CAG repeats, in case 1, the acute COVID-19 infection might represent the environmental modifier with the potential to influence the expression of intermediate alleles, promoting the development of HD [2, 5].

Continued monitoring of short- and potentially long-term implications in COVID-19 survivors, even in those only mildly affected clinically, as well as further knowledge about the immunogenicity of COVID-19 vaccines, are critical steps to develop a comprehensive strategy in providing resources and capacity in the healthcare system to face this pandemic.

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Data availability The authors take full availability of all materials described in the manuscript; all relevant data will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Declarations

Ethical approval We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work.

Consent for publication Both patients have given their consent to anonymously report their clinical reports in accordance with current ethical standards.

Conflict of interest G.P. has received a speaking fee from Lusofarmaco and Zambon. A.D.F. has received honoraria from Sanofi Genzyme and Zambon for Scientific Advisory Board and invited lecturers. R.C. has received a speaking fee from General Electric, UCB pharma, Lusofarmaco, Abbvie. A.F. and E.U. have nothing to report.

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