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CASE REPORT

Opsoclonus-Myoclonus-Ataxia Syndrome Due to Covid-19

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Abstract
Opsoclonus-myoclonus syndrome (OMS) as a rare neurological encephalopathic entity associated with non-specific infections or cancer processes has been repeatedly described in the setting of SARS-CoV-2 infection. We report a case of a 53-year-old man with SARS-CoV-2 infection, who developed clinical features of opsoclonus-myoclonus ataxia syndrome including cognitive impairments with a prolonged course of disease. Of particular note, cerebrospinal fluid (CSF) analysis revealed the production of myelin oligodendrocyte glycoprotein (MOG) antibodies, suggesting an underlying neuroimmunological mechanism associated with infection with the novel SARS-CoV-2 virus.

Keywords SARS-CoV-2 · Parainfectious disease · Opsoclonus myoclonus ataxia syndrome · Myelin oligodendrocyte glycoprotein

Dear Editor,

In addition to the primary medical and epidemiological challenges, the SARS-CoV-2 pandemic has triggered a vivid research activity on the organic dysfunctions associated with the virus known as Covid-19, and numerous investigations have been undertaken aiming to capture and refine the pathogenetic features of this virus [1]. In addition to cardiorespiratory and haemastaseological organ manifestations, the effects of the virus on neuronal tissues of the peripheral and central nervous systems have increasingly been observed and discussed [2–4] including direct pathogenic activities of SARS-CoV-2 predominantly in the brain, and immunologically mediated mechanisms [5]. The peripheral nervous system is frequently involved in the form of Guillian-Barré syndrome-like acute polyneuritis, and the central nervous system may be affected in the form of a multifocal encephalitis as well as myelitis [2, 3, 5]. According to a recent review, most cases of CNS syndromes in relation to SARS-CoV-2 are immunologically mediated disorders [6]. In analogy to other established parainfectious neurological diseases, detailed functional-analytical investigations, i.e. neurophysiological, radiological and laboratory chemical investigations, are necessary to establish a presumed causal relationship between a neurological manifestation and SARS-CoV-2 infection, if not to prove it. Over the past two and a half years, in addition to numerous systematic studies, a large number of individual cases of neurological disease as a result of SARS-CoV-2 infection have been reported. Interestingly, opsoclonus-myoclonus syndrome (OMS) as a rare disease has been repeatedly reported in association with SARS-CoV-2 infection [7–18]. Here we present an additional case of acute central nervous movement disturbance suggesting cerebellar disorder secondary to acute SARS-CoV-2 infection.

A 54-year-old man with a negative neurological history was admitted to hospital with respiratory symptoms. A few days earlier, he had tested positive for SARS-CoV-2 antigen. The patient's general condition deteriorated with fever, progressive respiratory insufficiency, opsoclonus and generalised myoclonic jerks. Covid-19 pneumonia was then diagnosed by computed tomography and the patient was transferred to the intensive care unit, where full heparinisation and treatment with dexamethasone were initiated. Symptomatic

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treatment of myoclonus with levetiracetam and clonazepam was initiated and later supplemented with valproic acid due to inadequate symptom control. Additional pharmacological treatment with clonidine and nepresol was given to control arterial blood pressure. In addition to a gradual stabilisation of respiratory function, a moderate improvement of myoclonus and opsoclonus was initially achieved. However, the patient developed a delirious state with agitation, oral automatisms and pronounced grimacing. After the patient's general condition became increasingly stable, he was transferred to a neurorehabilitative treatment, where myoclonia and orofacial dyskinesia, but also ataxia of stance and gait, and cognitive imairments, were still present. Further reduction of myoclonus was achieved by increasing the dose of valproic acid and clonazepam. Due to unsatisfactory clinical control of the intermittent oromandibular myoclonia with significant speech and swallowing impairment, trihexphenidyl was added. With this triple therapy, extensive symptom control of the oromandibular myoclonia was achieved, allowing a gradual dose reduction of clonazepam without recurrence of symptoms. Neuroradiological examination showed calcifications within the basal ganglia, wide perivascular spaces and morphological features of cerebral microangiopathy, but no evidence of inflammatory changes on MRI. EEG showed no hypersynchronous activity but intermittent focal rhythm slowing in the theta spectrum frontoparietally bilaterally. CSF analysis was positive for MOG Ig-G antibodies (1:80), although there was no pleocytosis, and oligoclonal bands were negative. Clinical neurorehabilitation focused mainly on ataxia, but also on hypertonic dysarthria, aphasia and fluctuating cognitive impairment, mainly in the attentional domain, resulting in marked improvements in both motor, i.e. ataxia and myoclonus, and neurocognitive skills. The patient was discharged home with a walker as a temporary mobility aid.

The present case illustrates an opsoclonus-myoclonus syndrome (OMS) in connection with a SARS-CoV-2 infection, which has been rarely reported before by other authors in the course of the Covid-19 pandemic. A causal relationship between OMS and the SARS-CoV-2 infection or the clinically definable Covid-19 in the present case can be assumed, not only because of the temporal relationship [19], but also with regard to the CSF-analytical proof of antibody production against neural myelin protein (myelin oligodendrocyte glycoprotein; MOG). The striking cognitive impairment in the present case is in line with numerous clinical observations of a parainfectious encephalopathy with an OMS following viral infection [9, 20]. OMS is characterised by a variable combination of opsoclonus, i.e. irregular, involuntary and arrhythmic eye movements in horizontal, vertical and diagonal directions, and myoclonus, characterised by sudden and brief spasms of multiple muscles resulting in jerky movements [21]. In addition, cerebellar ataxia is one of the clinical features of this entity, and cognitive impairments such as aphasia or attention problems have been reported on several occasions [20]. Chan et al. [22] recently reported a systematic review, identifying 51 patients from surveys on reports published from November 1, 2019, to December 6, 2020. As a result, myoclonus and cerebellar ataxias had an acute onset, usually within 1 month of COVID-19 symptoms. Among these 51 patients, 23.5% (12 out of 51) of cases had myoclonus and cerebellar ataxias, 35.3% (18 out of 51) of cases had myoclonus without cerebellar ataxias and 41.2% (21 out of 51) of cases had cerebellar ataxias. Myoclonus was multifocal or generalized, activated by action in 56.7% (17 out of 30) cases and by sensory stimuli in 46.7% (14 out of 30) of cases. Myoclonus and cerebellar ataxias were concurrently associated with other neurologic symptoms, including cognitive changes (45.5%) or a Miller Fisher syndrome variant (21.2%). Chan's findings correspond to the clinical features of ataxia, myoclonus with the peculiarity of additional priming by action or sensory stimuli and finally cognitive impairment in the present patient.

OMS is a rare disease with a predominantly paraneoplastic or parainfectious aetiology associated with a wide range of viral infections [23–29]. Associations with anti-Ri or anti-ANNA-2 antibodies have been reported in paraneoplastic cases of extracranial solid tumors [6, 30, 31]. However, as a reliable diagnostic immunological marker has not yet been found, a significant number of patients cannot be definitively diagnosed and are often diagnosed as having idiopathic OMS [27, 32, 33]. Nevertheless, OMS was rarely reported as a case of central nervous system (CNS) involvement with SARS-CoV-2 during the Covid-19 pandemic. Of note, the causal mechanisms of CNS involvement after SARS-CoV-2 infection are still under discussion, including direct virus-mediated tissue damage, a secondary pathway due to systemic effects such as hypoxia or cerebrovascular injury, but also tissue damage due to autoimmune mechanisms [3, 5] seems to play a crucial role. The finding of MOG-specific antibody production identified in the present case is interesting, as MOG-specific antibodies have been repeatedly reported in cases of encephalitis following SARS-CoV-2 infection [19, 34, 35], but with different clinical and radiological features, including cognitive impairment, paresis and sensory disturbances, and diffuse cerebral hyperintensities and leptomeningeal enhancement on MRI. Observations in the patient reported here and in another paediatric case of MOG antibody-positive OMS following SARS-CoV-2 infection [36] suggest that OMS may be a rare manifestation of MOG antibody-associated encephalitis. MOG antibodies have been found in CNS inflammatory diseases following a variety of systemic infections, suggesting that SARS-CoV-2 infection with Covid-19 may have been an immunological trigger for MOG antibody production in our case [6, 37]. The normal CSF laboratory parameters observed in the present case are consistent with the majority of reports of SARS-CoV-2 infection with neurological disorders [2, 6, 10, 11, 17, 18, 38]. In addition, normal brain MRI findings

in patients with neurological disorders including OMS associated with SARS-CoV-2 infections have been described in several reports (e.g. overviews of [6, 38], and also [19]).

Considering the diversity of autoantigens reported in OMS in the absence of a disease-specific antibody marker [32], OMS is thought to be caused by cerebellar degeneration following neuroimmunological processes against various surface targets [39]. Notable, MOG-specific antibodies have been shown to have a high affinity to cerebellar surface antigens [40], supporting the notion of a causal role for MOG antibodies in the present case. MOG-antibody production has been observed in several cases of acute neurological diseases such as acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD) or transverse myelitis (MY) associated with SARS-CoV-2 infection [6], even at low MOG antibody titres (1:160) and normal cell counts in CFS [41]. Immunosuppressive treatments with steroids, intravenous immunglobulins or monoclonal antibodies such as rituximab have been successfully administered in such cases [9, 11, 12, 16, 18, 19, 27] and were considered in our case of OMS. However, as it has been reported in the majority of reported patients suffering OMS in association to Covid-19 ([12, 18, 22]; but see also [38], with clinical recovery just in 12 of 34 cases), the clinical course in our patient was favourable and the combined symptomatic treatment of myoclonus with levetiracetam, valproic acid, clonazepam and finally trihexphenidyl ultimately proved effective, as in similar cases [13, 42], thus avoiding the need for prolonged immunosuppressive treatment after the initial administration of steroids. In addition to pharmacological treatment, neurorehabilitative approaches focusing on oromandibular and speech coordination, but also on posture and gait in the face of ataxia appear equally relevant for a favourable functional outcome.

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Data Availability No datasets or materials can be accessed.

Declarations

Ethical Approval The authors confirm that the approval of an institutional review board was not required for this work. A written informed consent of the patient was obtained for the publication of his data. The authors have read the journal's position on issues involved in ethical publication and affords that this work is consistent with those guidelines.

Competing Interests The authors declare no competing interests.

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