

Parainfectious autoimmune encephalitis related to SARS-COV-2 infection, presented with catatonia

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ABSTRACT

SARS-CoV-2 infection commonly affects both the central and peripheral nervous systems. As a result of this effect, different neurological and psychiatric clinical pictures emerge. Although it is known that the neurotropic effect of this new microorganism is high, its effects on neuronal structures in the short and long term are still controversial. Neurological involvement secondary to SARS-CoV-2 is heterogeneous in terms of both clinical presentation and treatment responses and prognosis.

In this study, a case of encephalitis developing after SARS-CoV-2

infection is presented. In the case, classical catatonia and encephalopathy clinic were observed together. The emergence of the neuropsychiatric clinic after the symptoms of SARS-CoV-2 infection disappeared, suggesting that, the picture is primarily related to immune processes. The presented case showed a good clinical response to symptomatic catatonia treatment and immune modulatory agents and recovered both physically and cognitively without any sequelae. In terms of clinical presentation and treatment response, it is thought that SARS-CoV-2 infection creates a distinct and unique encephalitic involvement from the usual forms of autoimmune encephalitis.

Key Words: SARS-CoV-2; Catatonia; Encephalitis; Autoimmunity

INTRODUCTION

Autoimmune encephalitides are a group of syndromes characterized by subacute onset, impairment of consciousness, memory, and/or behavior, psychiatric disorders, seizures and movement disorders. Various etiologies including remote malignancies and infectious agents are known to cause autoimmune encephalitis, and the cause is undefined in some cases [1]. Psychiatric manifestations, such as psychosis, panic attacks, compulsive behavior, euphoria, fear, and catatonia, are observed early in the course of autoimmune encephalitis [2]. Catatonia is a state of psychomotor immobility and behavioral abnormality, mainly linked to psychiatric disorders [3-5]. It is also associated with many etiologies, including, but not limited to, metabolic, autoimmune, toxic, infectious, and neoplastic processes [6]. Non-psychiatric causes of catatonia make up 20% of all cases.

Soon after the first SARS-CoV-2 cases were reported in Wuhan, China, neurologists have started analyzing and discussing the immediate effects of SARS-CoV-2 on the central nervous system [7-9]. Encephalitis is amongst one of the most frequently seen central

nervous system diseases during or after the SARS-CoV-2 infection [10-13]. The disease mechanisms leading to encephalitis are linked to either autoimmune processes or direct viral invasion in patients with SARS-CoV-2 infection [14-17]. In this case report, we present a patient who developed probable parainfectious autoimmune encephalitis during the course of SARS-CoV-2 infection. The patient presented in this paper differs from the previously reported autoimmune encephalitis cases in terms of the associated neuropsychiatric findings.

CASE PRESENTATION

A 61-year-old female patient was brought to the Emergency Room (ER) by her family members. The patient developed fatigue, cough, and fever seven days before her admission to the ER. SARS-CoV-2 Polymerase Chain Reaction (PCR) test positivity was detected in the nasopharyngeal swab sample taken because of the aforementioned complaints. Since pneumonia was not observed in thorax Computerized Tomography (CT), she was given a five-

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day favipravir treatment and later followed up at home without hospitalization. The patient's symptoms associated with SARS-CoV-2 infection had ameliorated within a few days under the favipravir treatment.

On the fifth day of SARS-CoV-2 treatment, her relatives observed a noticeable difference in her speech and they mentioned that the patient had begun to speak at a rather unusually slow pace. Clinical symptoms showed rapid progression in the following two days, resulting in a clinical picture comprised of mutism, negativism, gait and balance impairment, involuntary jerky movements in all extremities and trunk, paucity in voluntary motor movements, and generalized stiffness.

There was no known chronic disease or medication use in the patient's history. She is a non-smoker. There was no history of toxin exposure. The patient, who is a high school graduate, retired from civil service a few years ago. She had neither history of cognitive impairment nor a psychiatric disorder necessitating use of any psychiatric medication. There was no family history of either neurological or psychiatric disease.

During her neurological and psychiatric evaluation at the ER, the patient was awake and oriented to time, place and persons. Cooperation was poor and her response to commands was delayed and slow. Spontaneous movements were very few and she had shown resistance to the examination, which were ascribed to lack of initiative and negativism. She merely answered to the questions asked by the physicians. During the examination, the patient exhibited grimace and a scared facial expression. There were no signs of meningeal irritation. Cranial nerves were intact and muscle strength was normal. Deep tendon reflexes were found to be increased globally. Bilateral ankle clonus was noted. Extrapyramidal system examination revealed bilateral symmetrical bradykinesia and rigidity, which was more prominent in the upper extremities and axial muscles. The patient tended to keep her left arm flexed at 90 degrees at the elbow joint and posturing was observed. Generalized myoclonus and enhanced startle reaction evoked by audible stimuli were noted. The patient also described visual hallucinations in the form of animals wandering around. Severe truncal and gait ataxia were observed. Considering the history of SARS-CoV-2 infection and clinical findings together, the clinical picture was diagnosed as catatonia due to organic etiology. Bush-Francis Catatonia rating scale score was calculated as 20/69.

Regarding vital signs and laboratory findings of the patient, heart rhythm was regular. Blood pressure and body temperature values were noted to be in the normal range. Her breathing was comfortable and her respiratory rate was normal. Kidney and liver function tests and electrolyte values were within normal limits. There was borderline leukocytosis and c-reactive protein elevation at the time of evaluation. D-dimer and fibrinogen values were moderately high. No pathology was observed in unenhanced cranial CT and contrast-enhanced cranial MRI performed under

emergency conditions. Electroencephalographic examination showed diffuse slow wave abnormality. SARS-CoV-2 PCR, which was positive seven days ago, was repeated and found to be negative. Lumbar puncture was performed for differential diagnosis of encephalitis. Cerebrospinal Fluid (CSF) opening pressure was measured as 180 mm/water. CSF glucose was within normal limits with respect to serum glucose level (83 mg/dl - 105 mg/dl). CSF protein was 48 mg/dl. In the CSF, 30 leukocytes/mm³ dominated by lymphocytes were detected. The IgG index was calculated as 0.86. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, adenovirus, parvovirus B19 and enterovirus PCR in CSF were negative. SARS-CoV-2 PCR was also found negative in CSF.

CNS infection was excluded based on the findings in structural brain imaging, electrophysiological examinations and CSF analysis. Empirical treatment was planned with the diagnosis of probable autoimmune encephalitis and 1000 mg intravenous methylprednisolone was started. Following a test-therapeutic dose of 1 mg lorazepam, the patient's rigidity improved significantly. This response was considered to support the diagnosis of catatonia, and the lorazepam dose was gradually increased to 1 mg six times a day. 1000 mg intravenous levetiracetam was added daily for the symptomatic treatment of generalized myoclonus.

On the third day of the treatment, rigidity, myoclonus, abnormal facial expression, negativism, and mutism were no longer observed. However, when the patient attempted to stand up and walk, severe postural instability was evident. The mini-mental test score was found to be 15/30. Attention and working memory were preferentially affected. At this stage, brain FDG-PET/MRI and whole-body FDG-PET/CT were performed. Brain FDG-PET/MRI showed marked hypometabolism in bilateral frontal and inferior parietal cortices. Whole-body FDG-PET/CT did not disclose any pathological finding that could indicate a malignancy, which would lead to the diagnosis of an incidental paraneoplastic disorder. Paraneoplastic antibodies (anti-yo, anti-ri, anti-hu, anti-amphiphysin, anti-PNMAA2/Ta and anti-CV2.1) and autoimmune antibodies (AMPA1, anti-AMPA2, anti-NMDA, anti GABA B1, anti-CAPR2 and anti-LGI) were all negative.

On the tenth day of 1000 mg intravenous methylprednisolone treatment, neurological examination of the patient was found to be normal other than moderate cognitive impairment. Mini-mental test score was 23/30. In the control electroencephalographic examination, the bioelectrical slowing was found to be improved. It was decided to continue the treatment with 1 mg/kg oral methylprednisolone, because of the ongoing cognitive impairment. Lorazepam and levetiracetam treatments were stopped, since the symptoms of catatonia and myoclonic jerks disappeared.

One month after the onset of the clinical symptoms, a standardized neuropsychometric test was performed. The examination showed minimal defects in the attention and

retrieval processes. Since the patient was reported to be anxious during the test procedure, psychiatric counseling was requested and psychotherapy without pharmacotherapy was recommended. Oral methylprednisolone treatment was scheduled to be stopped following gradual tapering within the next month. Regular follow-up and malignancy screening was recommended because of the risk of recurrence of the encephalitis and exclusion of the coincidental paraneoplastic etiology.

DISCUSSION

In the presented case, neurological and psychiatric symptoms developed during the course of a SARS-CoV-2 infection. Infectious central nervous system involvement was not considered, since the symptoms of SARS-CoV-2 completely resolved and the SARS-CoV-2 PCR was negative during the ER admission. Based on the clinical and imaging findings, the patient's clinical picture was attributed to parainfectious autoimmune encephalitis secondary to SARS-CoV-2 infection. Favourable clinical response to empirical intravenous methylprednisolone treatment supported the diagnosis. The benefit observed with the administration of lorazepam also supported the diagnosis of catatonia.

Catatonia is considered a heterogeneous disease in terms of etiology and clinical course. However, good response to benzodiazepine or electroconvulsive therapy in most cases of catatonia indicates the existence of a common pathophysiology. Rogers claimed that the neurovegetative properties of catatonia are related to innate and acquired immune system activation [18]. The observations reported in this case report are consistent with their hypothesis. Catatonia has been rarely reported in the course of autoimmune encephalitis due to the SARS-CoV-2 infection [19,20].

In the literature, cases of autoimmune encephalitis developing after HSV-1 infection and with positive anti-NMDAR antibodies have been frequently reported [21]. EBV, HHV-6, adenovirus and enterovirus are known as viral infectious agents causing anti-NMDAR encephalitis. The same viral agents have been shown to cause encephalitis associated with AMPAR, GABAAR and GABABR antibodies, as well as anti-NMDAR antibodies. A similar post-viral autoimmune process is thought to be triggered in cases of encephalitis that develops during or after SARS-CoV-2 infection. So far, no known autoimmune antibodies have been detected in cases of SARS-CoV-2 associated encephalitis. It is yet to be discovered whether this reversible picture, which responds well to immunomodulatory therapy and symptomatic approaches but does not cause any structural brain damage, is a new type of autoimmune encephalitis triggered by SARS-CoV-2 infection.

CONCLUSION

In this study, a case of parainfectious autoimmune encephalitis developed after SARS-CoV-2 infection is presented. The most striking feature of the case is the co-occurrence of classical catatonia symptoms and encephalopathy. With immunomodulatory therapy and symptomatic catatonia treatment, the patient was treated physically and cognitively without any sequelae.

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