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THE FIRST MANIC EPISODE POST-COVID-19 OF A PATIENT WITH TUBEROUS SCLEROSIS: CASE REPORT[1]

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ABSTRACT

After the COVID-19 turned into a pandemic, it was revealed that the disease affected many systems, including neuropsychiatric systems. Depression, anxiety, post-traumatic stress disorder and psychosis depending on viral infection and medical therapy might be observed. Although neuropsychiatric diseases such as seizures, mental retardation and autism are seen in tuberous sclerosis, bipolar disorder and mania are very rarely reported together with tuberous sclerosis. A 36-year-old male patient with no known neuropsychiatric disease was admitted to our hospital with the development of extrapyramidal side effects after receiving antipsychotic treatment in the primary health care hospital due to his first manic episode after COVID-19. The patient was diagnosed with tuberous sclerosis owing to his skin lesions and cranial images. His symptoms were brought under control after medical therapy. Probable etiologies of the case coming with the first manic episode post- COVID-19, are direct or indirect effects of the virus, medical therapy(methylprednisolone) being applied, and/or factors depending on tuberous sclerosis. The patient was considered as the first manic episode due to steroids use because of the emergence of his complaints after steroids, improvement of clinical findings 2 weeks after the onset of antipsychotic and mood stabilizer treatment, and the absence of a medical history of bipolar disorder. Other causes such as tuberous sclerosis and indirect effects of the virus were considered as predisposing factors. Our case is the first case in the literature because a patient with tuberous sclerosis had his first manic episode after COVID-19. It should be kept in mind that the

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etiologies underlying psychotic symptoms which develop following COVID-19 may depend on several reasons.

Keywords: COVID-19, Mania, Steroids, Tuberous Sclerosis

COVID-19 SONRASI İLK MANİK ATAK İLE BAŞVURAN TUBEROSKLEROZLU HASTA: OLGU SUNUMU

ÖZ

COVID-19'un pandemiye dönüşmesi sonrası hastalığın nöropsikiyatrik sistemler dahil birçok sistemi etkilediği ortaya çıkmıştır. Viral enfeksiyona ve verilen tedaviye bağlı depresyon, anksiyete, post travmatik stres bozuklukları ve az bir oranda psikoz görülebilmektedir. Tuberoskleroz de benzer şekilde epilepsi, mental retardasyon ve otizim gibi nöropsikiyatrik bulgular görülmesine rağmen eşlik eden bipolar bozukluk ve mani sonra derece nadir bildirilmiştir. Olgumuzun hem tuberoskleroz olması hem de COVID-19 sonrası ilk manik atağını geçirmesi nedeni ile sunulmuştur. Bilinen nöropsikiyatrik hastalığı olmayan 36 yaşında erkek hasta geçirdiği COVID-19 sonrası ilk manik atak nedeni ile dış merkezde antipsikotik tedavi alması sonrası ekstrapiramidal yan etkiler gelişmesi üzere hastanemize başvurdu. Cilt lezyonları ve beyin görüntüleri nedeni ile ek olarak tuberoskleroz tanısı konuldu. Olgunun medikal tedavisi sonrası semptomları kontrol altına alındı. COVID-19 sonrası ilk manik atağı ile gelen olgunun muhtemel etiyolojileri virüsün direk veya indirek etkisi, aldığı medikal tedavi veya tuberosklerozise bağlı durumlardı. Olgu, şikayetlerinin steroid sonrası ortaya çıkması, tedavisine antipsikotik ve duygudurum düzenleyici başladıktan 2 hafta sonra klinik bulgularının düzelmesi, ailesinde ve kendisinde geçirilmiş bipolar bozukluk öyküsü olmamasından dolayı steroid kullanımına bağlı ilk manik atak olarak değerlendirildi. Olgunun tuberoskleroz olması ve virüsün indirek etkileri gibi diğer sebepler yatkınlık sağlayan etkenler olarak düşünülmüştür. Olgumuz tuberoskleroz olan bir hastanın COVID-19 sonrası ilk manik atağını geçirmesi nedeni ile literatürdeki ilk vakadır. COVID-19 sonrası gelişen nöropsikiyatrik semptomların altında yatan etiyolojinin birçok nedene bağlı olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Bipolar, COVID-19, Manik Atak, Psikozis, Steroid, Tuberoskleroz

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INTRODUCTION

Emerging in China and transforming into a pandemic in a short time, SARS-CoV-2, also known as Coronavirus Disease-2019 (COVID-19), infected approximately 140 million people and caused a 3-million death toll (WHO, 2021). Neuropsychiatric syndromes might be seen as a result of both direct or immune system mediated indirect effects of viral infections over the central nervous system (Rogers et al., 2020; Tomonaga, 2004). Delirium is the most seen neuropsychiatric symptom post-COVID-19. Followed psychiatric disorders are depression, anxiety, post-traumatic stress disorder and less frequently psychosis (de Sousa-Moreira et al., 2021). Psychotic disorders and mania might develop in relation with medical treatment or through psycho-social stress disorder or viral exposure (Brown et al., 2020; Mawhinney et al., 2020; Proudfoot et al., 2011).

Tuberous sclerosis is a rare autosomal dominant neurocutaneous disease with neuropsychiatric disorders such as mental retardation, epilepsy, autism and hyperactivity. Concurrence of bipolar or mania and tuberous sclerosis has been reported only in a few cases. The relation between either concurrence has not been assessed clearly due to lack of cases (Chopra et al., 2006; Gupta & Haria, 2015).

In this case report, a newly diagnosed tuberous sclerosis patient who had his first manic episode post-COVID-19 and developed extrapyramidal side-effects after antipsychotic treatment will be presented. Our case is the first case in the literature because a patient with tuberous sclerosis had his first manic episode after COVID-19.

CASE REPORT

Working as a cook, the 39-year-old male patient, married with four children and poorly-educated (having left primary school), was living with his family. As a result of the nasal PCR performed after the patient applied to the hospital on 11th March, 2021, with complaints of fever, dyspnea and fatigue, he was diagnosed with COVID-19. He had ICU (Intensive Care Unit) treatment for four days since there is COVID-19 lung involvement in his chest CT (computed tomography) (Figure 1). 250mg methylprednisolones was applied for two days, reduced gradually in two weeks and then discontinued. After the patient was discharged from ICU, complaints of increase in goal-directed activities, briskness, over speaking, decrease in sleep started. Several days after leaving the hospital, the patient applied to the emergency service with these complaints. The patient was intramuscularly injected haloperidol 5 mg and biperiden 2 mg and was prescribed haloperidol 5 mg/d, biperiden 2 mg/d and quetiapine 50 mg/d. Having thought that his complaints didn't disappear, the patient applied to a neurologist. A treatment of 25 mg fluphenazine depot intramuscular injection was applied to the patient and chlorpromazine 100mg/d was prescribed. The patient took chlorpromazine 100 mg/d, biperiden 2 mg/d and haloperidol 5 mg/d for about ten days. Although there is a decrease in initial complaints, complaints of restlessness, walking with small steps, sweating and trembling in legs started. With these complaints, the patient was hospitalized in the psychiatry clinic. In his psychiatric examination, it was detected that his speech speed and amount increased, flow and rhythm of thought accelerated, his mood became euphoric, psycho-motor activities increased and sleep amount decreased. Neither he nor his family didn't have a psychiatric disease history.

Young mania rating scale was 30, and Clinical Global Impression-Severity Form was 5. In his physical examination facial angiofibroma, periungual and subungual fibroma in hands and feet, shagreen patch in waist (figure 2) were detected. As to neurological examination, bradykinesia, bradymimi, rigidity in right extremity and akathisia were detected. The patient's mood disorder was considered as the first manic episode. Extrapyramidal side-effects were thought to develop secondarily depending on anti-psychotic drugs. His treatment was rearranged as biperiden 4 mg/d, propranolol 40 mg/d, quetiapine 200 mg/d, lorazepam 3.75 mg/d. Following the cranial MRI (Magnetic resonance imaging) performed for etiological investigation, cortical and subcortical tubers and subependymal nodules were detected (figure 3). EEG (electroencephalography), renal ultrasound, retinal and cardiac examination carried out for tuberous sclerosis investigation were normal. The patient was diagnosed with tuberous sclerosis for his skin findings (angiofibroma, ungual fibroma, shagreen patch) and cranial images (subependymal nodules, cortical and subcortical tubers) meet five major findings of tuberous sclerosis diagnosis criteria, two of which are sufficient for diagnosis. As the result of the Wechsler Adult Intelligence Scale-R (WAIS-R) performed to measure the mental capacity of the patient, mild mental retardance was detected (verbal IQ: 68, performance score IQ: 61, full scale score IQ: 63). During follow-up, extrapyramidal symptoms subsided within a week, biperiden and propranolol were gradually reduced and then discontinued. Olanzapine 5mg/d was added due to continuing manic symptoms such as increased psycho-motor activities, pressured speech and euphoric mood. During follow-up, olanzapine was raised to 15 mg/d and quetiapine to 250 mg/d; and as mood stabilizer, 600mg/d lithium was added to the treatment and then raised to 900 mg/d. Lorezapam was discontinued gradually due to the reduction of the manic symptoms of the patient who had a regular sleep pattern. Young mania rating scale was 10 and Clinical Global Impression-Severity Form was 2 on the 20th day of the hospitalization. The patient was discharged to be examined later.

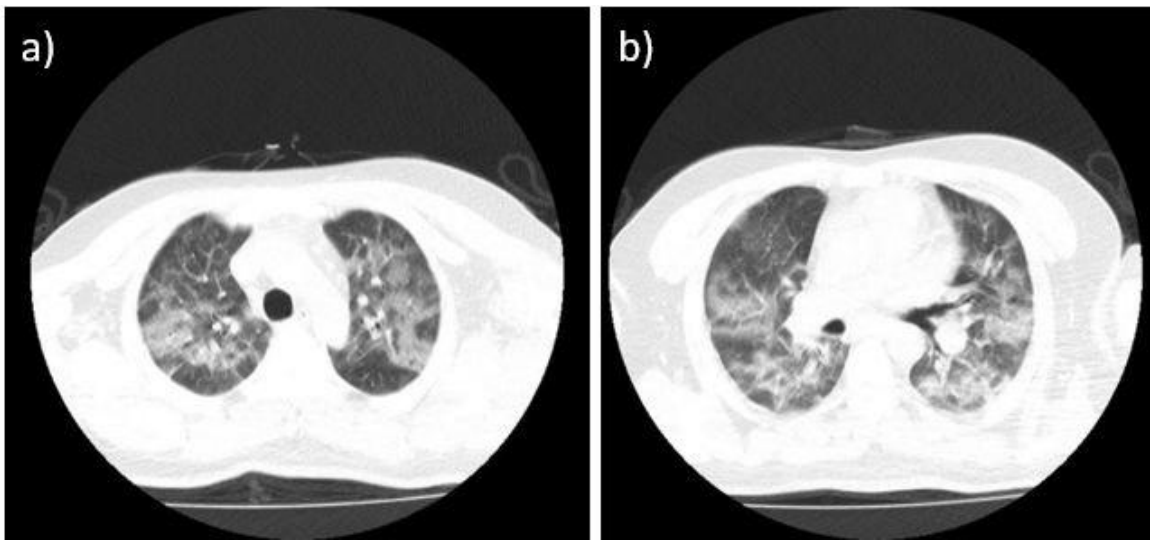

Figure 1. Involvement Compatible with COVID-19 in Both Lung Lobes

Figure 2. Figure "a" and "b", Angiofibroma on Face, Figure "c" Periungual and Subungual Fibroma, Figure "d" Shagreen Patch at the Waist of Patient

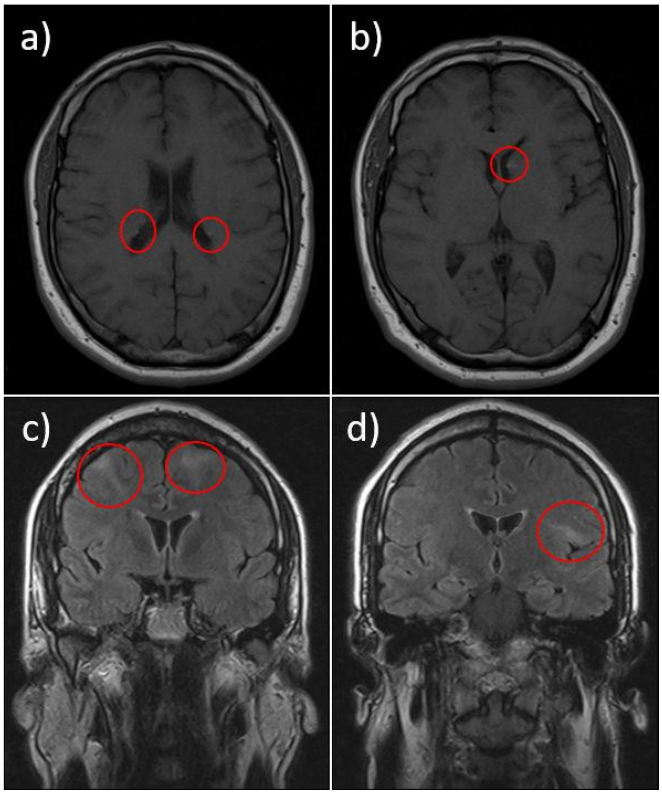

Figure 3. Figure "a" and "b" Subependymal Nodules in T1 Cranial MR Images, Figure "c" and "d" Cortical and Subcortical Tubers in T2 Cranial MR Images

RESULTS

In this study, we present the first manic episode post-COVID-19 of a patient who was newly diagnosed with tuberous sclerosis. Both tuberous sclerosis and COVID-19 have been associated with psychotic disorders and mania (Chopra et al., 2006; Haq et al., 2009; Mawhinney et al., 2020; Rogers et al., 2020). Psychiatric disorders such as psychosis and mania post-COVID-19 are considered to develop depending on direct or indirect effects of the virus over central nervous system, on medical treatment or psycho-social stress (Brown et al., 2020; Proudfoot et al., 2011). COVID-19 might invade the brain by using the olfactory nerve and the cells by using the ACE-2 receptor (Arbour et al., 2000). ACE-2 receptors existing on the glial cells and neurons constitute a potential target for the coronavirus and could cause neuropsychiatric syndromes (Baig et al., 2020). The virus could exercise its indirect effect through secondary hyper-inflammatory syndrome, para/post-infectious inflammatory or immune mediated systems (Mehta et al., 2020; Severance et al., 2011). It has been found in various studies that pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-a) play a role in the pathogenesis of bipolar disorder (Steardo & Verkhratsky, 2020). The major hallmark of the disease is the cytokine storm characterized by elevated levels of inflammatory cytokines, mainly IL-6 and TNF-α (Shekhawat et al., 2021). Since the brain imaging was normal in our patient, the direct effect of the virus was not considered. However, we cannot exclude psychiatric diseases that may develop due to the indirect effects of the virus such as cytokines.

In COVID-19 treatment, Steroids therapy is suggested in order to prevent cytokine storm especially for patients receiving high oxygen support (Alcock & Masters, 2021). Approximately 60 % of the patients might show psychiatric syndromes after steroids therapy such as depression (35 %), mania (31 %), psychosis (14 %), delirium (13 %) and mixed states (6 %). The frequency of psychiatric syndromes is directly proportional to steroids dose. 1.3 % of the patients receiving a steroids dose less than 40 mg/d, 4.6 % of the patients receiving 41 to 80 mg/d and 18.4 % of the patients receiving 80 mg/d or more are detected to experience psychiatric disorders. Most psychiatric symptoms start to occur in six weeks after the onset of steroids use and recover completely in six weeks, as well. The recovery duration has been detected to be 19.3 days in average for mania and psychosis (Dubovsky et al., 2012). Our patient was hospitalized in ICU due to dyspnea five days after COVID-19 diagnosis. In ICU, 250 mg/d methylprednisolones was applied and gradually discontinued within two weeks. A week after the steroids use, manic episodes started. Our case has been considered as the first manic episode depending on steroids use as the clinical symptoms recovered two weeks after the onset of anti-psychotic treatment and mood stabilizer, and neither he nor his family didn't have a medical history of bipolar disorder.

Although neuro-psychiatric syndromes such as depression, hyper-activity, autism and epilepsy might be frequently seen along with tuberous sclerosis, bipolar disorder with tuberous sclerosis has been rarely reported. There could be several mechanisms that can explain the relation between tuberous sclerosis and bipolar disorder. First of all, a relation has been detected between locations of brain lesions and psychiatric conditions. Right hemisphere, cortical and subcortical lesions have been shown to be in relation with manic episode. Besides, another

possible relation is genetic (Chopra et al., 2006; Haq et al., 2009). The fact that there are bilateral multiple cortical and subcortical tubers in the patient's right hemisphere is compatible with bipolar disorder mechanism associated with lesions. However, since the patient didn't have a medical history of bipolar manic episode and he had a manic episode post- COVID-19 following steroid use, we thought that the manic episode stemmed mainly from steroid use.

CONCLUSION

More than one mechanism could underlie neuro-psychiatric syndromes developing after Coronavirus. It was hard to detect the actual etiology because our case had both tuberous sclerosis and COVID-19, received steroids as medical treatment and experienced intense emotional stress in ICU. According to our literature review, our case is the first one regarding the concomitant diseases. Clinicians thus had better bear in mind several parameters while approaching the manic episode during COVID-19 pandemic.

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