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Suspected Amyotrophic Lateral Sclerosis Post COVD-19 infection

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease involving the degeneration of cortical and spinal motor neurons, with specific sparing of sensory neurons. While the majority of ALS cases are sporadic, genetic susceptibility leading to familial ALS is well established. The etiology of ALS remains, at large, unknown, although environmental exposures and infections have been implicated. (ALS could be sporadic or familial).

We present a patient who developed ALS-like symptoms following an acute COVID-19 infection. These symptoms include a combination of upper motor neuron (UMN) and lower motor neuron (LMN) damage involving the brainstem and multiple spinal cord innervation regions. Magnetic resonance imaging (MRI) studies of the brain and spinal cord along with extensive laboratory studies were negative and helped exclude syndromes that mimic ALS. Furthermore, electromyogram (EMG) abnormalities showed fasciculation potentials (FPs) and spontaneous denervation discharges which are indicative of reinnervation. These finding along with clinical abnormalities on physical exams, represent the hallmark of the disease, and are standard criteria to the diagnosis of ALS in our patient.

We present a case of acute, early-onset, sporadic ALS following COVID-19 infection in otherwise healthy male.

Keywords: *Amyotrophic Lateral Sclerosis; COVID-19; Electroencephalogram; Upper Motor Neuron; Lower Motor Neuron; Fasciculation; Denervation; Reinnervation*

Abbreviations

ALS: Amyotrophic Lateral Sclerosis; PD: Parkinson Disease; NMDA: N-Methyl D-Aspartate; SOD1: Superoxide Dismutase 1; HIV: Human Immuno-Deficiency Virus; MRI: Magnetic Resonance Imaging; ACE2: Angiotensin-Converting Enzyme 2; QHS: Quaque Hora Somni; PCR: Polymerase Chain Reaction; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

Introduction

Amyotrophic Lateral Sclerosis (ALS), also known as "Lou Gehrig's disease", is a neurodegenerative disease primarily affecting the motor systems of the cortex, brain stem, and spinal cord. The incidence is estimated to be about 1/100,000. About 5 - 10% of the reported cases are familial, and the rest are sporadic (reference). Most recently, genetic mutations in the gene encoding zinc-copper superoxide dismutase on chromosome 21q22.11 have been identified in familial ALS, and it is the first gene to be reported [1]. Other risk factors have been reported which include, for example, abnormal RNA processing, disorders of protein quality control, excitotoxicity, and cytoskeletal derangements. Early on, viral infections were implicated in the etiology including infections with Enterovirus [2-4], however, the exact mechanism has yet to be delineated.

ALS results in a combination of damage to both upper and lower motor neurons. Degeneration of the ventral motor horn gives rise to lower motor neuron signs and symptoms of ALS. These may include weakness, gait disorder, reduced reflexes (flaccid paralysis), muscle atrophy and fasciculations. Degeneration of the lateral corticospinal tract gives rise to the upper motor neuron signs. These may include signs and symptoms of movement stiffness, slowness and incoordination, spasticity and hyperreflexia (spastic paralysis). Bulbar upper motor neuron degeneration gives rise to signs and symptoms of dysarthria, dysphagia, pseudobulbar affect (inappropriate laughing, crying or yawning). Cognitive and behavioral changes involving frontotemporal executive dysfunction may be characteristic as well. It is important to note that the presentation of ALS varies from person to person. The presentation is dependent on the specific motor neurons affected. Symptoms of ALS are commonly asymmetric, beginning in the distal extremities (hands, feet) and, over time, progressive weakness spreads to other parts of the body. As the degeneration of motor neurons advances, muscles progressively get weaker and weaker. Neuromuscular respiratory failure, typically, develops within three to five years of symptom onset, and is considered the leading cause of mortality. ALS is therefore considered one of the most severe motor neuron diseases.

Common environmental and genetic factors have been established for different neurological disorders, including Parkinson's disease (PD), frontotemporal dementia, and ALS. Research has suggested a shared etiology of both Down syndrome and SOD1-related ALS disease, due to their tau hyperphosphorylation. Treating patients with PD, ALS, and dementia with the same treatment has been tested in clinical trials. Further understanding of how these disease/treatment mechanisms are connected may play a key role in improving treatment and management for patients. To date, Riluzole is currently the only FDA-approved drug treatment identified to have been proven beneficial in the survival of patients with ALS. Riluzole is known to trigger presynaptic inhibition and thus release glutamate from cerebrocortical nerve terminals. It inactivates voltage-gated sodium channels and is a noncompetitive NMDA receptor antagonist.

Materials and Methods

A left-handed, 57-years-old Hispanic male with past medical history of lumbar disc herniation and hyperlipidemia presented at the end of July 2021 with three months of simultaneous and gradually progressive generalized weakness of upper and lower limbs, especially at the end of the day, accompanied with tingling sensations in the lower extremities. He complained of difficulty in grasping objects, ambulation, and maintaining balance. He suffered at least four falls since the weakness onset. Furthermore, the patient appreciated and complained of generalized muscle twitching (fasciculations) and involuntary limb movement. His symptoms developed within 2 - 3 weeks after being infected with COVID-19.

On neurological examination, higher mental functions were intact. There was no history suggestive of dysphagia, dysarthria, or sensory abnormalities. Cranial nerves II-IIX were intact. On motor system examination, patients had increased tone in the bilateral upper and lower extremities with weak grasp strength bilaterally. A bilateral postural resting tremor, that was more evident on the right, was appreciated. Patient also displayed pronator drift on the right. Muscle fasciculation was present in the bilateral upper and lower extremities, left more than right. Muscle strength of the right and left deltoid and right and left bicep was ⅘. The left and right tricep were found to be full strength. The strength of pronation of the right and left forearm was ⅘. The remainder of the strength exam showed full 5/5 throughout all muscle groups both proximally and distally. Posture was found to be stooped, however, walking and tandem gait tests showed no abnormalities. Cerebellar functions were intact with no ataxia appreciated. There was no action tremor appreciated on the finger nose finger test. The patient had a negative Romberg test. Deep tendon reflexes were found to be 3+ throughout with an upgoing plantar reflex bilaterally. Hoffman's sign was positive bilaterally. Muscle bulk of upper and lower limbs was normal, however, bilateral clonus of the ankle and knee was found. Horizontal nystagmus was noted when testing lateral gaze. The patient's vitals were within reference range and there were no significant findings found when examining all other systems. Of note, serology for human immuno-deficiency virus (HIV)-1, HIV-2, and syphilis was found to be non-reactive. The patient was scheduled for a follow up visit at the end of September 2021. At that time, the patient's chief complaint was severe left shoulder pain (rate the pain 0/10) with associated burning pain in the neck. The pain was chronic in nature and was not relieved by medications.

Brain magnetic resonance imaging (MRI) revealed no evidence of intra or extra-axial masses, hydrocephalus or abnormal extra-axial fluid collections. Cervical MRI showed multilevel cervical spondylosis and disc disease with desiccated central disc herniations indenting

the sac from C3-C4 level down to C6-C7 level, with no overt cord compression. Furthermore, it was suggestive of mild multilevel foraminal narrowing related to degenerative Luschka's joint changes and prominent uncinate processes. Lumbar MRI showed minimal lumbar herniation related to degenerative disc disease.

In July 2021, electromyography studies of the bilateral upper and lower extremities were performed. Nerve conduction studies of the bilateral upper extremities displayed conduction abnormalities that were suggestive of mild carpal tunnel syndrome on the right. A repeat electromyography study was performed in September 2021. In that study, significant evidence of widespread active and chronic denervation was shown. This denervation was found across multiple muscles from different myotomes. Of the three limbs tested in our patient, fasciculations were present throughout. Sensory and motor nerve conduction studies showed no abnormalities in all four tested nerves. However, the motor component of the right peroneal nerve revealed a mild reduction of amplitude. These findings along with normal sensory responses and chronic denervation in the left genioglossus muscle are highly indicative of diffuse motor neuron disease. All other possible differential diagnoses for the patient's symptoms were ruled out, and he was ultimately diagnosed with clinically definite ALS. This diagnosis was based on the revised El Escorial World Federation of Neurology criteria. The patient's progressive upper and lower motor neuron symptoms and signs also met the fit in Gold Coast criteria for ALS. We speculate that COVID-19 infection was the cause of ALS in this patient. after we ruled out all the possible risk factors of ALS in the patient.

Following the diagnosis, the patient was prescribed rosuvastatin 10 mg QHS, cyclobenzaprine 5mg, alprazolam 0.25 mg, and duloxetine. It was our recommendation to use an orthotic assistive device to decrease his fall risk. He was started on pain medications to alleviate his shoulder and neck pain as well. The patient was also evaluated by neurosurgery for evaluation of his cervical spine lesions. He was advised to stop driving and seek physical therapy.

Results and Discussion

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by loss of motor neurons in the motor cortex, brainstem, and spinal cord leading to muscle weakness, disability, and eventually death. Even though the etiology of ALS is unknown, several potential mechanisms have been put forward which include viral infections. There are various studies highlighting the role of infectious agents in the causation of neurodegenerative diseases like ALS [1].

Other proposed mechanisms include abnormal RNA processing, disorders of protein quality control, excitotoxicity, cytoskeletal derangements, mitochondrial dysfunction, apoptosis, growth factor abnormalities, inflammatory responses, and others [2]. One important mechanism involves viral infections. Researchers reported that ALS has resulted after infection with various viruses, including Poliovirus, enterovirus, herpes viruses and exogenous and inherited retrovirus [3-6]. However, a clear etiologic relationship between ALS and viral infections is lacking, despite exhaustive studies. To date, no correlation between ALS and COVID-19 have been reported. Furthermore, there are reports that COVID-19 infection accelerated the progression of ALS with rapid functional decline in otherwise slowly progressive ALS [7]. We report a case of ALS diagnosed roughly two weeks following COVID-19 infection, confirmed by polymerase chain reaction (PCR). We believe this is the first case report that points toward the potential of COVID-19 to cause ALS.

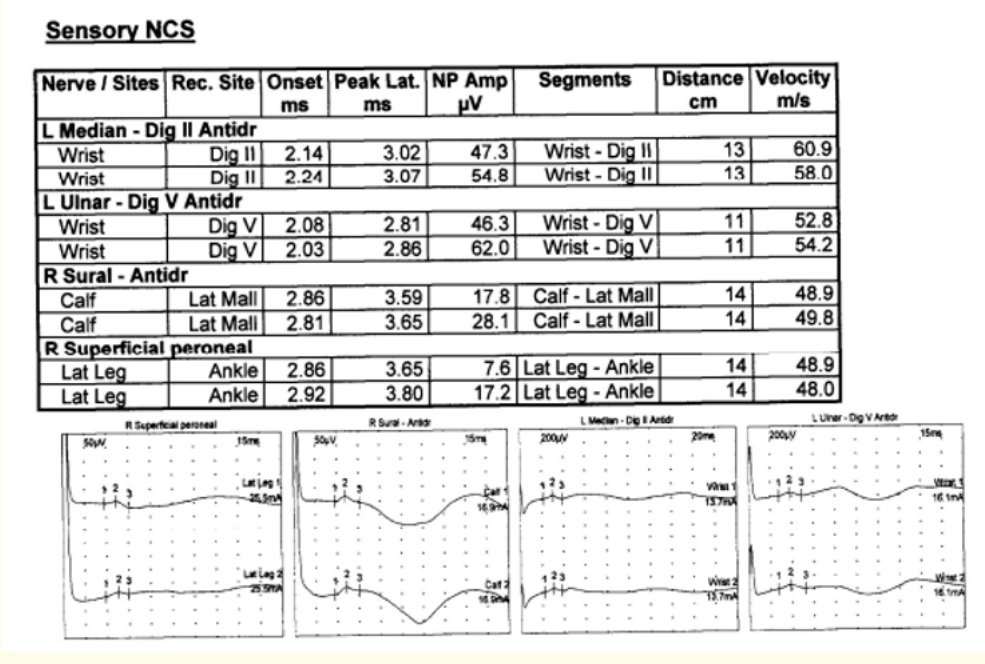
The neurologic manifestations including neuroinvasion, neurotropic, and neuroinflammatory events of COVID-19 infection have been well described recently [8,9]. These manifestations include encephalopathy, cerebrovascular disease, neuromuscular disease, meningoencephalitis, rhombencephalitis, and acute disseminated encephalomyelitis. The neuropathogenesis attributed to these manifestations are hypothesized to be neurologic injury from systemic dysfunction, renin-angiotensin system dysfunction**,** immune dysfunction, and direct viral invasion of the nervous system**.** We believe that the same mechanism induced by SARS-CoV-2 infection could lead to neurodegenerative changes in the CNS. Thus, giving rise to various neurodegenerative diseases including ALS.

Parameters	Lab values
eGFR	103 ml/min/1.73m^2
Sodium	142 mmol/l
Potassium	4.3 mmol/l
Chloride	105 mmol/l
Carbon dioxide	24 mmol/l
Calcium	10.4 mg/dl
Total protein	7.4 g/dl
Albumin globulin ratio	1.7
Total bilirubin	0.3 mg/dl
Alkaline phosphatase	64 U/L
ALT	25 U/L
AST	21 U/L

Table 1: *Routine laboratory workup.*

All values were within reference range.

A sensory nerve conduction study (Figure 1) of the peripheral nerves was performed to directly assess sensory axons. This study records a sensory nerve action potential (SNAP) proximal or distal to the site of stimulation. The patient's study displayed no conduction abnormalities.



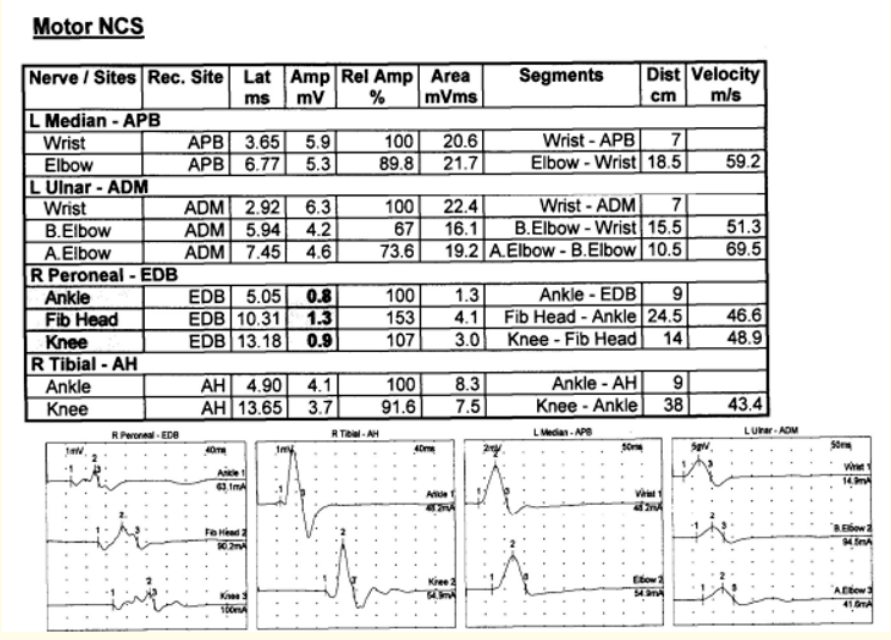
Sensory NCS

Nerve / Sites	Rec. Site	Onset ms	Peak Lat. ms	NP Amp µV	Segments	Distance cm	Velocity m/s
L Median - Dig II Antidr							
Wrist	Dig II	2.14	3.02	47.3	Wrist - Dig II	13	60.9
Wrist	Dig II	2.24	3.07	54.8	Wrist - Dig II	13	58.0
L Ulnar - Dig V Antidr							
Wrist	Dig V	2.08	2.81	46.3	Wrist - Dig V	11	52.8
Wrist	Dig V	2.03	2.86	62.0	Wrist - Dig V	11	54.2
R Sural - Antidr							
Calf	Lat Mall	2.86	3.59	17.8	Calf - Lat Mall	14	48.9
Calf	Lat Mall	2.81	3.65	28.1	Calf - Lat Mall	14	49.8
R Superficial peroneal							
Lat Leg	Ankle	2.86	3.65	7.6	Lat Leg - Ankle	14	48.9
Lat Leg	Ankle	2.92	3.80	17.2	Lat Leg - Ankle	14	48.0

Figure 1: *Sensory nerve conduction study of the peripheral nerves*

Sensory nerve conduction studies directly assess sensory axons by recording a sensory nerve action potential (SNAP) proximal or distal to the site of stimulation. The patient's study displayed no conduction abnormalities (Suggestive of mild carpal tunnel syndrome on the right in September 2021?).

A motor nerve conduction study (Figure 2) was also performed. This study delivers an electrical stimulus to a specific skin location that is known to overlie a peripheral nerve. The motor responses are then recorded from muscles innervated by that nerve. The patient's motor conduction velocity of the L Median, L Ulnar, and R Tibial nerve segments were all within reference range. However, the motor conduction velocity of the R Peroneal nerve segment was found to be mildly reduced at the level of the ankle, fibular head, and knee.



Motor NCS

Nerve / Sites	Rec. Site	Lat ms	Amp mV	Rel Amp %	Area mVms	Segments	Dist cm	Velocity m/s
L Median - APB								
Wrist	APB	3.65	5.9	100	20.6	Wrist - APB	7	
Elbow	APB	6.77	5.3	89.8	21.7	Elbow - Wrist	18.5	59.2
L Ulnar - ADM								
Wrist	ADM	2.92	6.3	100	22.4	Wrist - ADM	7	
B.Elbow	ADM	5.94	4.2	67	16.1	B.Elbow - Wrist	15.5	51.3
A.Elbow	ADM	7.45	4.6	73.6	19.2	A.Elbow - B.Elbow	10.5	69.5
R Peroneal - EDB								
Ankle	EDB	5.05	**0.8**	100	1.3	Ankle - EDB	9	
Fib Head	EDB	10.31	**1.3**	153	4.1	Fib Head - Ankle	24.5	46.6
Knee	EDB	13.18	**0.9**	107	3.0	Knee - Fib Head	14	48.9
R Tibial - AH								
Ankle	AH	4.90	4.1	100	8.3	Ankle - AH	9	
Knee	AH	13.65	3.7	91.6	7.5	Knee - Ankle	38	43.4

Figure 2: *Motor nerve conduction study.*

This study delivers an electrical stimulus to a specific skin location that is known to overlie a peripheral nerve. The motor responses are then recorded from muscles innervated by that nerve. The motor conduction velocity of the L Median, L Ulnar, and R Tibial nerve segments were all within reference range. However, the motor conduction velocity of the R Peroneal nerve segment was found to be mildly reduced at the level of the ankle, fibular head, and knee.

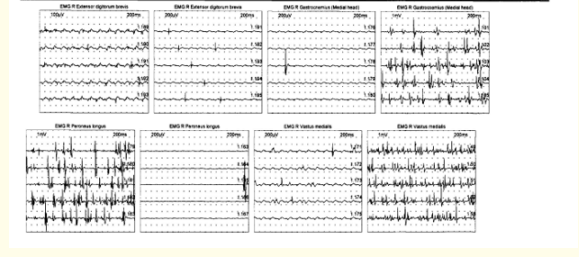
Finally, an electromyogram study (Figure 3), which includes an assessment of spontaneous activity, evaluation of motor unit amplitude, duration, and appearance; and recruitment pattern of the muscle was performed. The patient's study revealed significant evidence of widespread active and chronic denervation. These denervations were found across multiple muscles from different myotomes. Specifically, the R extensor digitorum braves, medial head of the gastrocnemius, L first dorsal interosseous, L Biceps brachii, and L Genioglossus were shown to be markedly reduced. Furthermore, of the three limbs tested, fasciculations were present throughout. These findings, along with relatively normal sensory responses, are highly indicative of diffuse motor neuron disease.

The temporal association between ALS and COVID-19 infection can be explained to greater extent based on evidence from other human and animal coronaviruses. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Of the known coronaviruses to date, at least three of them are neurotropic and neuroinvasive including severe acute respiratory syndrome coronavirus (SARS-CoV) [10,11]. SARS-CoV-2 shares origin, genomic sequence, nucleotide identity and mode of spread to intermediate host and human with other coronaviruses including SARS-CoV. Both SARS-CoV-2 and SARS-CoV bind angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells including the central nervous system. "ACE2 receptors are abundant in central nervous system (CNS) cells which

EMG

EMG Summary Table

			Spontaneous					MUAP			Recruitmen
Muscle	Nerve	Roots	IA	Fib	PSW	Fasc	H.F.	Amp	Dur.	PPP	Pattern
R. Extensor digitorum brevis	Deep peroneal (Fibular)	L5-S1	1-	2+	2+	1+	None	1+	1+	N	Reduced
R. Gastrocnemius (Medial head)	Tibial	S1-S2	N	None	None	1+	None	N	N	N	Reduced
R. Peroneus longus	Superficial peroneal	L5-S1	N	None	None	1+	None	N	N	N	N
R. Vastus medialis	Femoral	L2-L4	N	None	None	2+ (fast)	None	N	N	N	N
R. First dorsal interosseous	Ulnar	C8-T1	N	None	2+	2+ (fast)	None	N	1+	1+	N
R. Extensor carpi radialis longus	Radial	C6-C7	N	None	2+	2+ (fast)	None	N	2+	2+	N
R. Biceps brachii	Musculocutaneous	C5-C6	N	None	2+	2+ (fast)	None	N	1+	1+	N
L. First dorsal interosseous	Ulnar	C8-T1	N	None	3+	2+ (fast)	None	1+	2+	2+	Reduced
L. Extensor carpi radialis longus	Radial	C6-C7	N	2+	2+	2+ (fast)	None	N	N	N	N
L. Biceps brachii	Musculocutaneous	C5-C6	N	None	None	2+ (fast)	None	N	N	N	Reduced
L. Genioglossus	Hypoglossal	Medulla-	N	None	2+	1+	None	N	1+	1+	Reduced



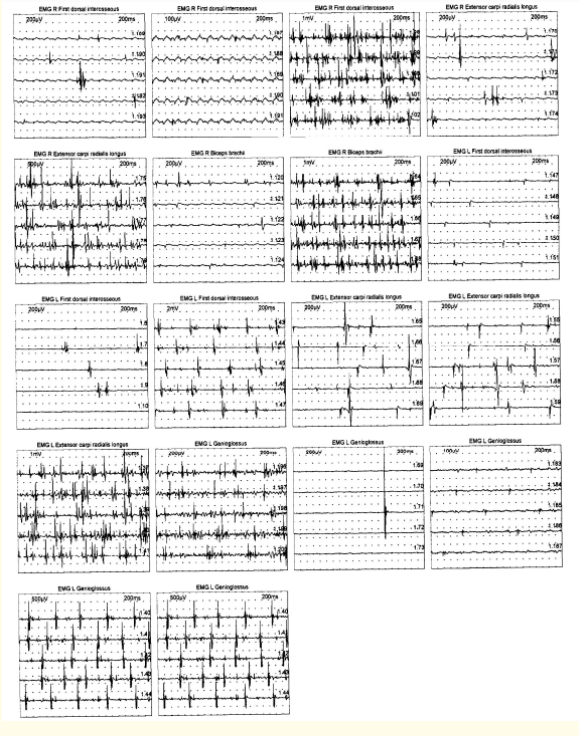


Figure 3: *Electromyogram study.*

Needle electromyogram includes assessment of spontaneous activity, evaluation of motor unit amplitude, duration, and appearance; and recruitment pattern of the muscle. The patient's study revealed significant evidence of widespread active and chronic denervation. These denervations were found across multiple muscles from different myotomes. Specifically, the R extensor digitorum braves, medial head of the gastrocnemius, L first dorsal interosseous, L Biceps brachii, and L Genioglossus were shown to be markedly reduced. Furthermore, of the three limbs tested, fasciculations were present throughout. These findings, along with relatively normal sensory responses, is highly indicative of diffuse motor neuron disease.

make them prime targets for infection by SARS-CoV-2". "Similar to SARS-CoV, SARS CoV-2 spreads via haematogenous dissemination and neuronal retrograde dissemination via peripheral nerves to enter the CNS." Furthermore, the replication pattern of SARS-CoV-2 is found to be similar to that of neuroinvasive animal coronaviruses [12]. It has been suggested that cytokine storms developed in response to SARS-CoV-2 might be operating in the CNS as well, potentially leading to neuronal damage and neurodegenerative changes [13]. Further evidence suggestive of neurodegeneration following viral infections come from similarities between viral infection-induced inflammatory events to those observed in early neurodegenerative conditions, including altered expression of proteins relevant to axonal transport and synaptic transmission [14,15]. The supportive evidence points to a possible infection etiology of ALS course, which would explain our findings.

Conclusion

In conclusion, viral infections including SARS-CoV-2 can trigger inflammatory reactions that initiate neurodegeneration and thus, neurodegenerative diseases like ALS can occur. The degree of neurodegeneration might be affected by an individual's epigenetic differences and genetic makeup. It should be noted that COVID-19 infection in ALS patients can rapidly progress the disease process [16-19]. Thus, close monitoring of the ALS patients infected with COVID-19 is advisable. Maximal COVID-19 vaccination seems to be the effective way to prevent various life-threatening manifestations and long-term sequelae of COVID-19 which may include neurodegenerative diseases like ALS.

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