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Case Report

SARS-CoV-2 Unmasked Amyotrophic Lateral Sclerosis in a Genetically Predisposed Young Subject

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Abstract

Background: SARS-CoV-2 infection can induce neuroinflammation and facilitate subsequent neurodegeneration increasing the risk of Alzheimer´s disease, Parkinson´s disease or amyotrophic lateral sclerosis (ALS). We report a young male that developed ALS after COVID-19.

Summary: A 35-year-old male without family history of ALS, after 10-day quarantine and symptom resolution of COVID-19, he noticed progressive left lower extremity with weakness while running and falls. Then, he showed decreased strength and motor dysfunction in left upper and right lower extremities. He was sent to our institution one year after symptom onset. Neurological examination and neurophysiological studies confirmed the diagnosis of definite ALS. A genetic analysis reported TBK1 gene variant c.1305T> A (p.Tyr435*) and the diagnosis of ALS related to pathogenic TBK1-Gene was established. No frontotemporal dementia features were observed in this patient. In a literature review no reported cases associating ALS with SARS-CoV2 infection were found. SARS-CoV-2 can cause neuronal damage by direct invasion with further effects on oxidative stress, neuroinflammation and neurodegeneration. However, the possibility that COVID-19 unmasked pre-symptomatic ALS in a genetically predisposed young subject cannot be ruled out.

Key Messages: We consider that in our case, SARS-CoV-2 infection unmasked familial ALS. However, neuroinflammation and later motor neurons degeneration might be considered in this case with rapidly progressive ALS.

Keywords: *Amyotrophic Lateral Sclerosis; Lou Gehrig's; COVID-19 and SARS-Cov-2*

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a late-onset neurodegenerative disorder characterized by rapid deterioration and selective death of motor neurons (MN) in the cerebral cortex, brainstem and spinal cord. The clinical features are attributable to the superimposition of motor deficit in upper motor neurons (UMNs) and lower motor neurons (LMNs) [1-4]. The onset of ALS is most frequently observed in adults between 55 - 75 years old, and the average age of diagnosis is 56 years. Manifestation of ALS is uncommon in patients below 40 years old.

ALS is considered a multifactorial disease where genetic, environmental, and biological factors play an essential role in disease development and onset. More than 20 genes have been associated with ALS, and 15% of patients present with one of the five most common mutations, including the hexanucleotide expansions in chromosome 9 open reading frame 72 (*C9orf72*), superoxide dismutase 1 (*SOD1*), TAR DNA-binding protein 43 (*TARDBP*), fused in sarcoma (*FUS*), and TANK-binding kinase 1 (*TBK1*) [5,6]. The *C9orf72* is the most frequently affected and accounts for 40% of familial ALS (*F*ALS) cases [7]. On the other hand, speculations have been made that all cases of ALS have at least a partial genetic implication [6]. There is a high overall heritability of ALS, estimated to be between 30-60% in sporadic ALS (*S*ALS) cases [8,9].

Different molecular pathways, including neuroinflammation, mitochondrial dysfunction, oxidative stress, and excitotoxicity, have been proposed to play a role in ALS pathogenesis [10]. RNA Binding Proteins (RBPs) dysfunction has been implicated in the pathogenesis of ALS. These proteins regulate and control all the steps of the RNA life cycle, from transcription to degradation [11]. Dysregulation of RBPs has been correlated with an alteration in RNA metabolism and loss of protein homeostasis, which might lead to death of MN [12,13].

The Coronaviridae family comprises enveloped positive-sense single-stranded RNA viruses capable of causing human infection. These include beta coronaviruses (CoV) MERS-CoV and SARS-CoV and the novel coronavirus SARS-CoV-2 that the World Health Organization named COVID-19 [14-16]. Throughout the pandemic, it has been seen that COVID-19 can cause a broad spectrum of symptoms. Regarding the nervous system, patients with severe disease during hospitalization may have exhibited ischemic or hemorrhagic stroke [17], epilepsy, myelopathy, encephalopathy [18], Guillain-Barré syndrome [19] as well as other diverse neurological manifestations [20,21], including fatigue, headache, dizziness, anorexia [18], syncope [22], seizures [23], confusion, insomnia [24], anosmia, ageusia, myoclonus [25], neuropathic pain, and myalgias. Neurodegenerative and demyelinating neurological disorders have been considered to develop shortly after COVID-19 infection or in Long-Haul COVID [26].

In this report, we present a young male patient who developed ALS just after COVID-19 symptom resolution. An electronic literature search of articles reported in English with patient case reports and/or scientific data with a possible association of ALS and COVID-19 was performed.

Case Report

A 35-year-old male without a family history of ALS started in march 2021 with COVID-19, characterized by general malaise, fever, headache and lower back pain. At the end of his 10-day quarantine and COVID-19 symptom resolution, he noticed motor dysfunction of the left lower extremity, which manifested as tripping and weakness while running. In the following months, he stopped running due to progressive gait disorder and frequent falls. He developed weakness in left upper extremity. Nine months later, decreased strength and motor dysfunction in right upper extremity and a neurologist suggested the possibility of MN disorder and sent the patient to our institution one year after symptom onset. The evaluation showed in upper extremities (UE) 4/5 proximal and 3/5 distal strength, and 4/5 proximal and distal lower extremity (LE) strength, fasciculations were observed in UE and LE and abdominal muscles. The gait accomplished with walker support was spastic with increased muscle tone in LE. Tendon reflexes were increased, and bilateral Hoffman, Tromner, Babinski, and Chadock reflexes were present. The tongue showed discrete atrophy with fasciculations, and a left palmomental reflex. No frontotemporal dementia (FTD) features were observed. The ALS Functional Rating Scale Score was 37/48. Electromyography and nerve conduction velocity studies fulfilled the El Escorial-Awaji-Shima Criteria for the diagnosis of definite ALS. Brain MRI (1.5 Tesla) revealed in FLAIR and T2 pulse sequences bilateral high-intensity areas in the pyramidal tract (Figure 1), cervical and lumbar MRI were normal. A DNA sample was collected, and 34 genes for associated variants with ALS, Frontotemporal Dementia, and Alzheimer's disease, plus a *C9orf72* panel, were evaluated. Genomic DNA from the sample was enriched for targeted regions using a hybridization-based protocol

and sequenced using Illumina technology. The analysis reported the gene TBK1 variant c.1305T>A (p. Tyr435*) heterozygous consistent with a predisposition to or diagnosis of definite ALS related to one pathogenic variant of TBK1-Gene.

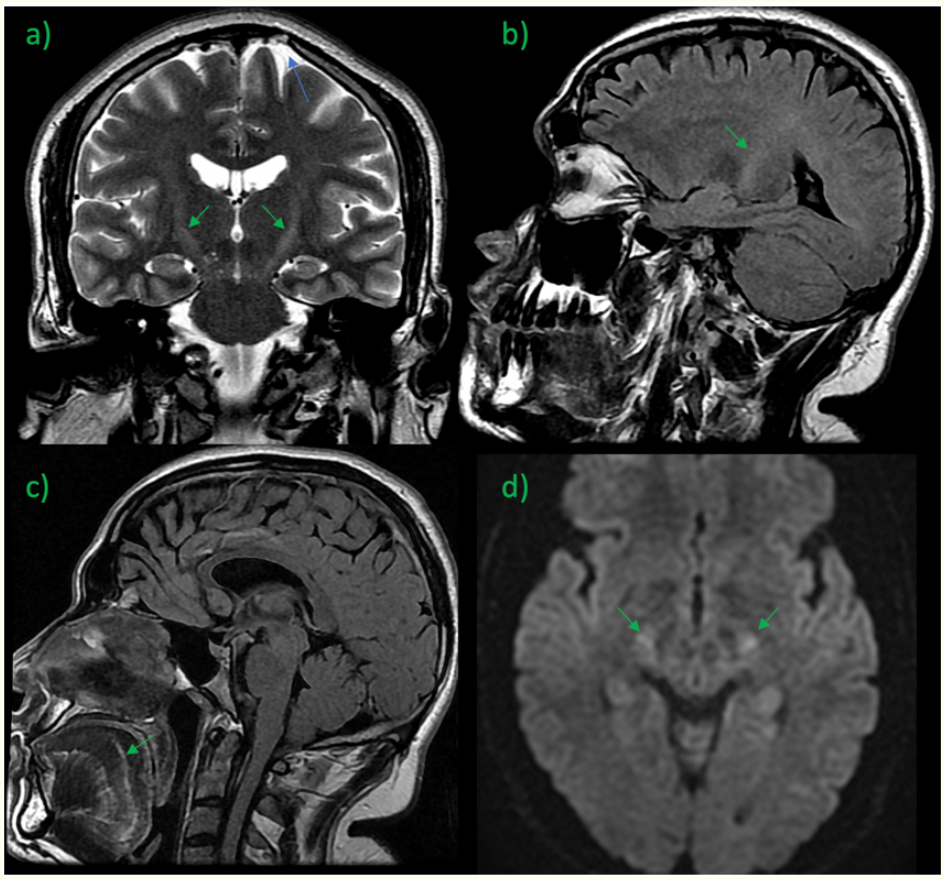

Figure 1: *Magnetic Resonance Imaging (a) T2 coronal view shows bilateral hyperintensity in the pyramidal tract (arrows), and brain atrophy (blue arrow), (b) T1-FLAIR sagittal view shows the high intensity signal in the pyramidal tract (arrow), (c) T1-FLAIR reveals the onset of high intensity signal in the tongue compatible with the "bright tongue sign" (arrow), (d) Diffusion weighted imaging, shows a spot of high intensity signal in pyramidal tract of the mesencephalic cerebral peduncle (arrows).*

Discussion

In this report, we describe a young patient that developed spinal ALS after COVID-19 infection, diagnosed by clinical and neurophysiological studies in a subject without history of FALS. This patient showed LMNs involvement however with predominant affection of UMNs, therefore these clinical findings are related to the bilateral high-intensity areas in the pyramidal tract observed in MRI (Figure 1). The genetic testing showed a TBK1 gene variant that has been reported to be associated with autosomal dominant FTD and/or ALS. SARS-CoV-2 infection yields neurological symptoms in mild and severe infections, and can induce neuroinflammation and subsequent

neurodegeneration increasing the risk of Alzheimer´s disease, Parkinson´s disease or ALS shortly after COVID-19 infection or in Long-Haul COVID [28].

It is possible that this RNA CoV causes a RBP dysfunction; modifying steps of the RNA life cycle, from transcription to degradation [11]. Therefore, dysregulation of RBPs and RNA metabolism might lead to MN death due to loss of protein homeostasis [12,13]. The pandemic showed a clinical progression and neurological deterioration of ALS patients who had a COVID-19 infection [28,29].

Many molecular mechanisms have been proposed and described in ALS, however, its pathogenesis remains uncertain. The COVID-19 virus has been described to possess a neurotropic potential with further effects on neuroinflammation, oxidative stress and immune system activation. The young ALS patient described in this report intends to question the relationship between COVID-19 infection and ALS onset in a genetically predisposed patient. SARS-CoV-2 can cause neuronal damage by direct invasion with further effects on oxidative stress, neuroinflammation and neurodegeneration. However, the possibility that COVID-19 unmasked pre-symptomatic ALS in a genetically predisposed young subject cannot be ruled out.

The main mechanism involved in *F*ALS and *S*ALS cases is RBP mislocalization from the nucleus to the cytoplasm, which promotes protein aggregation. The most distinctive neuropathological feature of ALS, present in more than 95% of cases, is a TDP-43 mislocalization from the nucleus to the cytoplasm of MN, which leads to cytoplasmic inclusions [12]. Abnormal autophagy has also been considered a pathogenic pathway for ALS. It has been recently seen that *TBK1* plays a role in central nervous system pathology since it is involved in diverse functions including: regulation of type I interferon (IFN) production, activation of several cellular pathways, autophagy of some pathogens and protein aggregates, and cellular homeostasis [30-33]. *TBK1* mutations leading to autophagy dysfunction have been proposed and identified as a possible pathogenic mechanism for ALS [34].

It has been considered that MN are particularly susceptible to the previously described molecular pathways altered in ALS due to their cellular properties and characteristics. MN are large-sized cells with a long and large-volume axonal compartment; hence, they have high metabolic demands and rely on optimal intracellular functions. MN depend on adequate mitochondrial function as they tend towards oxidative stress and are vulnerable to excitotoxicity and cellular dysregulation when mutations occur [10]. The SARS-CoV-2 might play a role in protein misfolding, which translates into protein aggregation in the brain, thereby possibly triggering neurodegenerative diseases including ALS [35].

Conclusion

Genetic, environmental, and biological factors play a role in ALS onset and development, but the relationship among these variables and how they affect each patient individually is unclear. We consider that in our case, SARS-CoV-2 infection unmasked fALS. However, neuroinflammation and later motor neurons degeneration might also be considered in this young patient with a rapidly progressive ALS.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Hector R. Martínez: Writing- review and editing, Supervision Carlos A. Arreola-Aldape: Writing- original draft, Investigation Jose A. Figueroa-Sanchez: Methodology, Writing- review and editing, Project Administration.

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