Multiple border zone infarcts and encephalopathy as clinical presentation of COVID19 in a patient with CADASIL

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ABSTRACT

Introduction: *The SARS-Cov-2 is associated with many neurological manifestations, including acute cerebrovascular disease. The most common reported stroke manifestation is ischemic stroke secondary to large vessels occlusion. The cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most frequent genetic disease associated with white matter disease and multiple lacunar strokes. How the SARS-Cov-2 could affect CADASIL patients is unknown. Our aim is to report the neurologic presentation of COVID19 in a CADASIL patient.* ***Method:*** *With searched laboratory data and patient history in clinical registers. Additional information was obtained from the neuropsychologic report and patient's family interview. Results: A patient on his fifties consulted to the emergency department for disorientation, difficulty with language and weakness of his right arm and leg. The magnetic resonance showed multiple acute subcortical border zone lesions and other chronic white matter lesions affecting the pole of the temporal lobes and external capsule, both typical of CADASIL. The genetic examination confirmed a missense mutation on the NOTCH3 gene. The patient was followed up for 10 months and although there was an improvement in his neurologic condition, he remained with cognitive deficits that impacted in his instrumental activities of daily living.* ***Conclusion:*** *CADASIL patients infected with SARS-Cov-2 can suffer of multiple border zone infarcts and encephalopathy. The COVID19 could accelerated the cognitive decline of CADASIL patients.*

Key words: *SARS-Cov2, CADASIL, ischemic stroke.*

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INTRODUCTION

The coronavirus outbreak started in December 2019 in China and rapidly propagated to other countries converting into a pandemic and a global threat[1]. The SARS-Cov-2 affects the pulmonary parenchyma, and it frequently presents with fever, malaise, cough and dyspnea[2]. The first case series of neurologic manifestations in hospitalized patients were published from the beginning of the pandemic. The frequency of neurologic manifestations varied between 57.4% in a Spanish case series and 36.4% in a Chinese case series[3,4]. In the Spanish case series, the frequency of reported cerebrovascular accidents was 1.7% while in the Chinese series was 2.8%[3,4]. In a French case series of 58 patients with severe respiratory distress, only one presented with an acute cerebrovascular accident and two others had subclinical lesions detected in brain images[5].

The Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most frequent genetic cause of cerebrovascular accidents (CVA) and dementia in adults. CADASIL patients suffer several neurologic manifestations as migraine with aura, cerebrovascular disease, depression, apathy, cognitive impairment and dementia[6]. The CVA and transient ischemic attack are the most frequent manifestations of CADASIL, being reported in 84% of a cohort of 8 French families and in 71% of a cohort of 28 German families and 1 Austrich family[7,8]. The mean age at stroke onset is reportedly 41-49 years and most of the patients present with typical lacunar syndrome manifesting as pure motor or pure sensory strokes, dysarthria or clumsy hand syndrome, and ataxic hemiparesis. Some patients show an insidious or stepwise evolution lasting up to several days[9].

We report the clinical case of a CADASIL patient with SARS-Cov-2 that presented with acute border zone lesions and encephalopathy.

CASE REPORT

A right-hand man of 51 years old presented to the emergency department after he developed three days prior to admission malaise, confusion, apathy, anorexia, expression aphasia and right brachial weakness. The patient had no past medical history of stroke, migraines, visual disturbances, or any neurological disease processes. His mother received treatment for multiple sclerosis and 3 of his 4 brothers suffered different neurologic diseases as cerebrovascular disease, migraine and cognitive decline buy none of them received a diagnosis of CADASIL. The physical examination revealed an inattentive, disorientate in space and time patient with hypofluent and agrammatical language associated with phonological paraphasias and right brachiocrural weakness. A non-contrast magnetic resonance image (MRI) of the head showed multiple frontoparietal border zone acute strokes as well as other acute strokes in the splenium of corpus callosum, temporal lobe, occipital lobe and right middle cerebellar peduncle **(see figure 1)** along with extensive chronic white matter signal abnormalities in the pole of temporal lobes and external capsule. The compute tomography angiogram of the brain and neck was normal. The echocardiography demonstrated mild dilatation of the left auricula, and the electrocardiogram was normal. The laboratory examination showed increased levels of protein c reactive (54.5 mg/L), ferritin (474 ng/mL), lactic dehydrogenase (443 U/L), urea (55mg/dl) and dimer D (1560.7 ng/mL). The chest computed tomography demonstrated frosted glass areas with foci of consolidation. An electroencephalogram (EEG) did not show electrical evidence of seizures but showed synchronic intermittent slowness activity in the frontal lobes. The levels of anticardiolipin, antiphospholipid, anti β-glucoprotein-1 antibodies, lupus anticoagulant, antinuclear antibodies, VIH and VDRL antibodies were in the normal range.

Two months after hospital discharge a neuropsychological evaluation demonstrated visual and verbal episodic memory impairment as well as immediate memory, working memory, attention, mental flexibility and visuospatial capacities alterations. During the next 10 month that the patient was followed up by the neurology

staff, he improved his cognitive condition and recovered his arm strength. However, he remains functional impaired in instrumental activities and was not able to return to work.

It is important to suspect other etiologies as demyelinating diseases but the presentation with aphasia and encephalopathy are infrequently on them. An autoimmune encephalitis was considered because of the patient age, language compromised and encephalopathy manifestations, but the cerebral images did not affect the cortex or the hippocampus. The Susac syndrome was also considered but our patient did not show the typical snowball lesions in the corpus callosum. Finally, the cardioembolic source was also suspected but the predominantly subcortical location of the lesions is quite uncommon in this syndrome. We thought about a CADASIL syndrome because of typical white matter lesions located in the pole of the temporal lobes and external capsule. A genetic examination confirmed a missense mutation in the NOTCH3 gene.

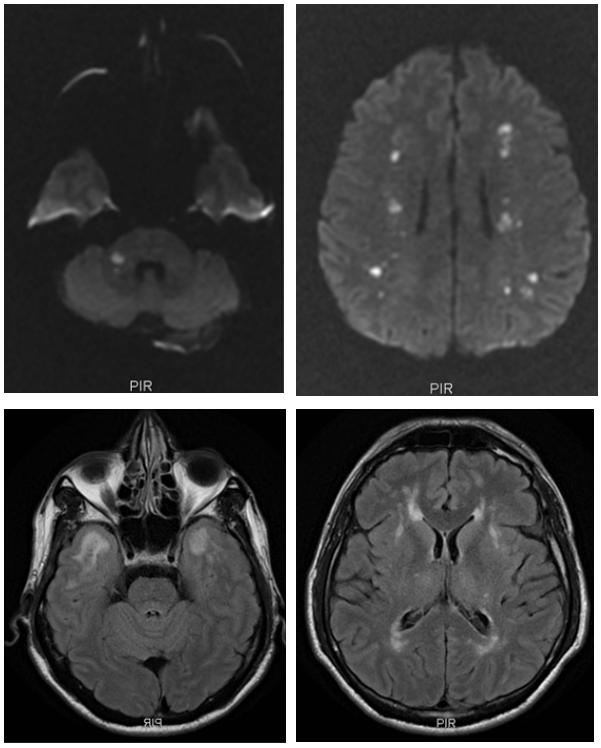

Figure 1. Upper left to right: DWI MRI sequence showing acute infarct in the right cerebellar peduncle; DWI MRI sequence showing multiple subcortical border zone lesions. Lower left to right: FLuid-Attenuated Inversion Recovery (FLAIR) MRI sequence showing white matter chronic periventricular and external capsule lesion; FLAIR MRI sequence showing chronic white matter lesions in the pole of the temporal lobes.

DISCUSSION

We reported a case of an asymptomatic patient with CADASIL that developed encephalopathy and multiple border zone infarcts after SARS-Cov-2 infection. Strengths of the current article include a detailed clinical, laboratory and image characterization. Besides, the patient received neuropsychological evaluation and was follow up for ten months. Among the possible limitations we did not carry out a lumbar puncture and did not order a perfusion brain study, both could help us to improve our understanding of the physiopathology of the patient' manifestations.

Other case reports of patients with CADASIL and COVID19 have been published in the literature before us. Trifan et al (2020) reported a 37-years-old African American female with prior medical history of hypertension, migraines without aura, history of cigarette smoking, and genetically proven CADASIL. The patient did not present typical COVID19 manifestations, but SARS-Cov-2 was detected in the swab of the hospital screening. MRI brain without contrast revealed an acute ischemic stroke in the right pons along with extensive chronic white matter signal abnormalities characteristic of CADASIL [(10)]. Williams et al (2020) reported a 38-year-old woman with mild dysarthria and a prodrome of 7 days of fever, myalgia, anosmia and ageusia. She had a family history of genetically confirmed CADASIL. The MRI revealed acute infarcts in eleven locations bilaterally within an internal border zone distribution and chronic small vessel disease characteristic of CADASIL[(11)]. Zhang et al (2020) reported a woman in her fifth decade of life that presented with dysarthria, dysphagia and

encephalopathy of two days before admission. The patient had no history of migraine, CVD, visual disturbances or any neurologic manifestation. At admission she had fever of 39°C and moderate respiratory distress. The MRI showed extensive white matter changes in the poles of temporal lobes, basal ganglia, external capsules and thalami. Some of these foci demonstrated diffusion-weighted imaging (DWI) changes and corresponding apparent diffusion coefficient (ADC)[12]. Noteworthy, the cases reported Zhang (2020) and Williams (2020) showed patchy border zone lesions as our patient and the case reported by Zhang presented also with an encephalopathy similar to our case report.

Different physiopathology mechanism could have contributed to the encephalopathy. Pugin et al (2020) reported 5 patients with acute respiratory syndrome secondary to SARS-Cov-2 presenting with a pathologic recovery of consciousness, which was responsive to glucocorticoids. These patients all presented with angio-MRI signs of inflammation of central nervous system arteries, consistent with an endothelialitis rather than a vasculitis. According to the authors, the encephalopathy could be secondary to a cytokine storm syndrome, exacerbated by increased endothelial dysfunction[13]. Furthermore, Pilotto et al (2020), evaluated the cerebrospinal fluid inflammatory profile of 13 patients with SASRS-Cov-2 encephalitis and found an increased level of several cytokines in the absence of SARS-cov-2 virus, consistent with an acute neuroinflammatory response and blood-brain barrier disruption[14]. On the other hand, a decreased brain perfusion could have contributed to the border zone lesions report in CADASIL patients with SARS-Cov-2. Helms et al (2020), reported bilateral frontotemporal hypoperfusion in all 11 patients who underwent perfusion imaging[5]. Evidence have showed that CADASIL patients have cerebral blood flow reduction[15] and decreased cerebral vasoreactivity[16] Consequently, the SARS-Cov-2 infection could worsen the already impaired cerebral hemodynamics of CADASIL patients and cause the reported border zone lesions.

In conclusion, we reported a CADASIL patient that after SARS-Cov-2 infection suffer encephalopathy and multiple bilateral border zone lesions, as other patients reported in the literature.

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