

Mechanisms of COVID-19-induced cerebellitis

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Mechanisms of COVID-19-induced cerebellitis

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Author contributions

MB, SOT, MS, MMA, FN, NDN, and AM have conceived and designed the concept and road map of the study, searched the literature, and drafted the manuscript. They designed the concept map and figures. *GJS* has critically reviewed the manuscript for its content, originality, English language usage, and interpreted data accuracy. *MSH* has designed the study, helped in manuscript preparation, and critically reviewed the manuscript. He is the archival author and attests to the integrity of the original data and the analysis reported in this manuscript. All authors have made a substantive contribution to approving the final manuscript.

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Abstract

The COVID-19 pandemic caused by SARS-CoV2 has raised several important health concerns, not least increased mortality and morbidity. SARS-CoV2 can infect the central nervous system via hematogenous or transneuronal routes, acting through different receptors including ACE2, DPP4 and neuropilin 1- and cause several issues, include the focus here, cerebellitis. The cerebellum is an essential part of the CNS located adjacent to the brainstem with a complex micro and macroscopic structure. The cerebellum plays several physiological roles, such as coordination, cognition, and executive functioning. Damage to the cerebellum can lead to incoordination and ataxia. In our narrative review, we searched different databases from 2021 to 2022 with the keywords cerebellum and COVID-19; 247 studies were identified and reviewed, focusing on clinical studies and excluding non-clinical studies; 65 studies were finally included for analysis. SARS-CoV2 infection of the cerebellum can be seen to be assessed through many methods such as MRI, PET, CT, post-mortem studies, and histological findings. These methodological studies have demonstrated that cerebellar infection with COVID-19 can bring about several sequelae: thrombosis, microbleed, hemorrhage, stroke, autoantibody production, ataxia, and widespread inflammation in the cerebellum. Such central effects are likely to exacerbate the known multi-organ effects of SARS-CoV2 and should also be considered as part of disease prognosis.

Keywords

Cerebellum, COVID-19, SARS-CoV2, Ataxia, Stroke

1. Introduction

The COVID-19 pandemic, which leads to mortality and morbidity caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is a worldwide concern [1,2]. Whilst SARS-CoV2 induces respiratory system impairment as seen for other coronaviruses, chronic and acute phases can also influence other fundamental organs like the brain and cause neurological symptoms such as headache, anosmia, and nausea [3]. The cerebellum is one of the most remarkable structures in the brain, involved in broad functions such as learning, coordination, and motor capabilities; however, it is currently unclear whether the cerebellum is involved in the CNS infectivity associated with COVID-19 [4,5].

Dissemination of SARS-CoV2 can cause neuronal necrosis and glial cell hyperplasia [6]. SARS-CoV2 can disseminate to the CNS through different pathways, including the transneuronal, hematogenous, olfactory bulb, serotonin-secreting dorsal raphe network, via a disrupted blood-brain barrier (BBB), and via the lymphatic systems. In addition to the pathways mentioned above, receptors like angiotensin-converting enzyme 2 (ACE2) or dipeptidyl peptidase-4 (DPP-4), neuropilin-1, as well as antibody-mediated pathways are the keys to virus admittance to the CNS [6-8].

Recent studies have shown that COVID-19 can be a cerebellitis-associated virus that can cause cerebellovascular disease, intracerebellar hematoma, and cerebellar bleeding [6-8]. Despite this, no clear correlation between COVID-19 and cerebellum infection has yet been evaluated. In this study, we review the involvement of the cerebellum in COVID-19 disease.

2. Methods

In this narrative review, we searched Embase, PubMed, SCOPUS, and WOS databases, using the keywords cerebellum and COVID-19, from May 10, 2021, to Aug 31, 2022. The studies' titles and abstracts were read to evaluate the inclusion criteria of the documents. We did not impose any limitations on language and study type. Descriptive information was collected from selected records. A total of 247 studies were evaluated. In this study, our inclusion criteria were cohorts, cross-sectional studies, case reports, and case series that included cerebellum and COVID-19 keywords in their research. The studies without clinical features were excluded. On this basis, 65 studies were included for analysis. Clinical features such as MRI, PET, CT, post-mortem characteristics, etc., were extracted for analysis.

3. Definition of cerebellum

The cerebellum is an evenly formed structure with a distinct neural arrangement based on stereotypes. The geometry of the cerebellum resembles a hemispherical ellipse with a central vermis and two adjacent hemispheres. The cerebellum's rostro-caudal contour is undulating due to the existence of transverse fissures. The pattern of fissures on the cortical surface of the cerebellum permits the identification of ten distinct lobules. Each of these lobules is associated with specialised brain-cerebellar functional loops. From a dorsal-ventral perspective, the cerebellar cortical array reveals three different layers. Purkinje cell dendritic arborization and inhibitory interneurons are seen in the molecular layer (basket and stellate cells). The Purkinje cell layer is generated ventrally by Purkinje cell somas and Bergman glia. The granular layer at the deeper cortical level comprises many granule cells controlled by Golgi, unipolar brush cells, and Lugaro neurons, as well as several types of glia. The axons of ascending granule cells divide into parallel excitatory fibres that connect the somas and dendrites of Purkinje cells [9,10].

The cerebellum is intimately involved in motor control, and cerebellar injuries result in the condition of movement incoordination known as ataxia. In addition to its role in cognition and executive control, the cerebellum influences diseases such as dyslexia and autism—the cerebellum functions as a forward controller that predicts the precise timing of related events through learning. The physiologic processes underlying cerebellar function continue to be the subject of intensive study. Signals entering the cerebellum via mossy fibers are processed in the granular layer and delivered to Purkinje cells, whilst a collateral channel stimulates the deep cerebellar nuclei (DCN). In turn, Purkinje cells inhibit DCN; therefore, the cerebellar cortex functions as a side-loop regulating DCN. It is now known that learning occurs through synaptic plasticity at multiple synapses in the granular layer, molecular layer, and DCN, expanding the original concept of the Motor Learning Theory, which predicted a single form of plasticity at the synapse between excitatory parallel fibers and Purkinje cells under the supervision of climbing fibers originating from the inferior olive. The precise modulation of timing and gain in the many cerebellar modules is the source of coordination [11].

4. COVID-19 and its sequelae

COVID-19, first described in Wuhan, China, in December 2019, brings about a syndrome similar to acute respiratory distress syndrome (ARDS), neurological and vascular complications, and vascular thrombosis [12]. Initial reports propose that 5%–20% of COVID-19-affected individuals advanced to a severe ailment categorized as a syndrome similar to ARDS [13–20]. COVID-19 is believed to comprise

an initial replication phase followed by immune dysregulation, and the latter has caused many patients to be hospitalized [21,22].

5. Imaging Studies of cerebellar effects of COVID-19

Although cerebellar brain damage is rare, its effects can be quite severe. Whilst the cerebellum is fairly protected from external forces, cerebellar damage often occurs due to neurodegenerative disorders, infection, drug abuse or anoxic brain injury. Cerebellar damage can result in substantial motor, cognitive and visual changes. COVID-19 virus is not restricted to the lung parenchyma [23]; therefore, the different types of brain imaging considered below may benefit patients with moderate to severe disease symptoms.

5.1. Positron Emission Tomography (PET) Studies; metabolism alterations.

Mild cerebellar hypermetabolism and cerebellar ataxia have been reported in COVID cases [24,25], reducing patients' quality of life. Despite this, hypometabolism has been seen in some patients; moreover, symptoms such as hyposmia, anosmia, ageusia, pain, sleeplessness, and cognitive and memory disorder are related to cerebellar hypometabolism [26]. In this regard, treatments, such as pulse corticosteroids or intravenous polyvalent immunoglobulins, have been proposed to treat cerebellar syndrome and cognitive impairment associated with COVID-19 [27].

Siripongsatien et al. [28] looked at individuals who reported neurological symptoms after receiving the COVID-19 vaccine. One of the assessed patients showed mild but meaningful decrements of perfusion in the bilateral cerebellum and bilateral thalamus in ^{15}O -water PET images. Semiquantitative and visual assessments indicated considerable metabolic alterations in occipital and parietal areas, regions involved in the fear network model, which have been linked to anxiety [28]. In acute, subacute, and chronic COVID-19 stages, Martini et al. examined brain metabolic dysfunctions and their correlations with neurological and biological parameters [29]. In the initial phase, the patients assessed longitudinally had extensive cerebral hypometabolism; after five months, the patients showed recovery [29]. Hypometabolism in the brain was associated with cognitive impairment, poor blood saturation, and an elevated inflammatory condition [29]. Over time, hypermetabolism remained in the brainstem, cerebellum, hippocampus, and amygdala and was linked with an inflammatory state [29]. Verger et al. collected PET scans of COVID-19 patients [30]; their study revealed variable hypometabolism of the olfactory bulbs in the fronto-basal area and related cerebral regions, such as the various brainstem, limbic/paralimbic regions, and the cerebellum. Morand et al.'s PET scans of paediatric and adult patients with long COVID [29] were

compared in the study. It was discovered that despite inferior initial severity at the acute phase of COVID-19 infection, after 5 months, paediatric patients showed the same brain hypometabolic pattern as adult long COVID patients, involving bilateral medial temporal lobes, the brainstem, and the cerebellum [31]. The PET study by Guedj et al. [30] showed brain hypometabolism in long COVID patients with biologically established SARS-CoV-2, with ongoing functional complaints beyond three weeks after the initial infection symptoms; scans showed that effects involved the olfactory gyrus and connected limbic/paralimbic regions, extending to the brainstem and cerebellum [32]. In a study by Guedj et al., [33]. PET scans revealed extensive bilateral hypometabolism, particularly in the olfactory/rectal gyrus, other limbic structures such as the hippocampus, amygdala, cingulate cortex, and parahippocampus, and the right superior temporal gyrus, the right pre-/post-central gyrus, hypothalamus, bilateral thalamus, medulla, pons, and cerebellum.

5.2. Magnetic Resonance Imaging (MRI) studies; the role of infarction.

Some COVID-19 patients show evidence of cerebellar infarction and lesions [34]; for example, MRI examination in a study on patients with acute ischemic stroke and COVID-19 showed acute infarcts in the right cerebellar hemisphere and acute left posterior inferior cerebellar artery territory infarction with petechial hemorrhage [35]. Moreover, in MRI of a patient with COVID-19, T2 lesions were seen in the right cerebellum [36]. In other studies, MRIs of axial T2 showed irregular signal changes in the cerebellar vermis and left cerebellar hemisphere due to posterior circulation infarctions [37]. In one study, injuries to the left cerebellar hemisphere were confirmed by MRI [38]. This study demonstrated acute and subacute infarcts using susceptibility-weighted imaging (SWI), an MRI procedure exquisitely sensitive to venous blood, hemorrhage, and iron storage. The same study confirmed multiple microhemorrhages in the left cerebellar hemisphere [38]. Moreover, brain MRI using gadolinium showed multiple acute ischemic infarctions in the regions of the left posterior inferior cerebellar artery, involving the left cerebellar hemisphere and the cerebellar vermis [37]. Injuries to the cerebellum and vermis can cause many severe disorders; for example, acute cerebellar injuries may cause a neurobehavioral syndrome requiring psychiatric interventions and concentrated neurorehabilitation [37]. Furthermore, some symptoms such as cognitive dysfunction, accompanied by executive functions, memory, and visuospatial abilities dysfunction, are linked to noticeable behavioral changes associated with the cerebellar cognitive, affective syndrome, which are reported in cases with acute cerebellar posterior lobe and vermis injuries [37]. In addition, some COVID-19 patients have shown acute cerebrovascular and neuropathologic deficits. These events can occur in Gray matter regions like the thalamus, putamen, pallidum, and cerebellum and can disrupt patient consciousness and arousal [39].

In some COVID-19 patients, diffusion limitation and fluid-attenuated inversion recovery (FLAIR) hyperintensity were apparent in several regions of the vermis and cerebellar hemispheres (10). An MRI study on six patients showed asymmetric and irregular FLAIR signals in the cerebellum, including cerebellar peduncles, in 4 cases [40]. In a survey by, Voruz et al., [38], post-COVID-19 patients underwent MRI scans and observed patterns of hypoconnectivity in parts of the right cerebellum. The presence of ACE-2 receptors in the cerebellum [41] may underlie the susceptibility of the cerebellum to SARS-CoV-2 injury [42]. Rastogi et al. [41] described a patient who acquired many neurological symptoms after receiving the AstraZeneca COVID-19 vaccination. The non-enhanced MRI sequences in the brain (including diffusion, susceptibility, T1, and T2-weighted FLAIR) revealed no gross abnormalities; however, there were frequent focal areas of contrast enhancement in the brainstem, deep grey matter, cerebral cortex, and cerebellum [43]. In reports by Shah et al. [42] the most frequent MRI T2/FLAIR imaging result was the presence of symmetric, multifocal lesions that invariably included the thalamus. The cerebral white matter, brainstem, cortical and subcortical white matter, and cerebellum were also frequently implicated [44].

In the research by Ciolac et al., [43], 1.5T magnetic resonance imaging (MRI) of the brain revealed bilateral, symmetrically distributed lesions in the infratentorial and supratentorial regions, with significant involvement of both cerebellar hemispheres and vermis. The lesions had a hyperintense signal on fluid-attenuated inversion recovery and diffusion-weighted images (limited diffusion), a hypo-hyperintense signal on T1-weighted pictures, and a hypointense signal on susceptibility-weighted imaging (hemorrhage) [43]. A hypointense signal on the apparent diffusion coefficient maps corroborated the limited diffusion characteristic of cytotoxic edema. On T1-weighted post-contrast pictures, there was a modest augmentation of contrast. The presented pattern was consistent with acute necrotizing encephalopathy caused by SARS-CoV-2 infection [45].

5.3. Computerized Tomography (CT) Studies; hemorrhagic evidence

Brain CT scans in COVID-19 patients verified acute large left cerebellar infarcts [35] and showed hemorrhages and low attenuation in the cerebellum [38]. In addition, CT scans have revealed multiple hypodense cerebellar lesions [46]. CT scans have also shown acute ischemic non-hemorrhagic infarcts in the vermis and cerebellar hemispheres due to an acute multifocal thrombosis in the posterior inferior cerebellar artery (20). It is assumed that the vessel blockade may have been caused by endothelial inflammation or increased coagulopathy after COVID-19 [47].

In Demir et al.'s research [48], a patient obtained CT pictures before being diagnosed with Fahr's syndrome and exhibited bilateral calcifications at the basal ganglia, nucleus dentatus, corona radiata, and cerebellum.

Due to co-infection with COVID-19 and tuberculosis, a head CT scan was performed on an Indian patient, which revealed a ring-enhancing lesion in the left cerebellar hemisphere with nearby edema producing effacement of the midbrain, 4th ventricle, and pons, resulting in obstructive hydrocephalus with supratentorial ventricular dilatation [49].

In a case report by Watanabe et al. [50] the clinical features of an exceptionally unusual case of myelitis with Guillain-Barré syndrome (GBS) and cerebellar ataxia (CA) following infection with COVID-19 were described. Despite the absence of abnormalities on brain MRI, SPECT revealed cerebellar hypoperfusion. The MRI of the spine revealed hyperintense lesions, mainly in the dorsal white matter, consistent with myelitis. Additional analyses of autoantibodies revealed the presence of anti-GM3, TPI, GluR, and NMDAR IgG antibodies in serum, as well as anti-GluR and NMDAR IgG antibodies with elevated granzyme B in CSF.

6. Direct dissemination to the cerebellum

6.1. ACE2 receptor; a trojan horse?

Coronavirus infection starts to develop within brain tissue areas such as the hypothalamus and then spreads to regions such as the cerebellum. The 'trojan horse' that the virus needs are associated with serine protease TMPRSS2 and ACE2 in the nasal epithelium [38]. By-products of angiotensin II metabolism, such as angiotensin IV and angiotensin 1-7, are the major causes of the COVID-19 disease pathogenesis [51]; however, there are contradictory data about the effect of these metabolites on brain tissues.

An important symptom that is proposed to be due to damage to the cerebellum by SARS-CoV-2 is ataxia [52], a spectrum of diseases that can cause movement deficit and disrupt everyday life. Further support for the hypothesis that the cerebellum is affected in COVID-19 disease is the appearance of SARS-CoV-2's RNA in the cerebellum [52].

6.2. Post-mortem studies demonstrated widespread inflammation.

Post-mortem studies on the effect of SARS-CoV-2 on the cerebellum and brainstem further support the hypothesis that these areas are affected in COVID-19. In the brainstem and cerebellum, diffuse activation of microglia with occasional microglial nodules was prominent, according to a study of the neuropathological features of the brains of 43 patients who died in Hamburg, Germany from COVID-19 infection [53]. Neuropathological studies involving immunohistochemical and histological staining, identified activated microglia, astrocytes, and cytotoxic T lymphocytes in the brainstem, basal ganglia, olfactory bulb, and cerebellum [54]. The study by Matschke et al. [53] also reported

dispersed stimulation of microglia, with sporadic microglial nodules in the cerebellum and brainstem. Overall, the existence of SARS-CoV-2 in the CNS was not directly attributed to the harshness of neuropathological alterations [53]. A thorough neuropathological explanation would be necessary to untangle which alterations are related to SARS-CoV-2.

Colombo et al. [55] described post-mortem microscopic and macroscopic alterations in COVID-19 patients. All patients found abnormalities in the cerebellum and cerebral cortex, predominantly in the right cerebellar hemisphere, as well as petechial hemorrhages in the grey and white matter, microglial and neuronophagia nodules. Infiltration of inflammatory cells (macrophages) into the perivascular regions of the cerebellum has also been reported [56]. In the study by Guedj et al., it was hypothesized that COVID-19's neurological effects may be the consequence of an immunological response to direct viral neuroinvasion or occur after therapies and involvement of organs [56]. Moreover, axonal injury associated with changes in neurofilament scaffolding functions, axonal radial architecture, and the creation of axonal spheroids were reported [56]. In line with previous studies, a loss of neurons was seen in the granule cell layer, and complete fading of internal granular cell layer neurons was observed. It was proposed that oxygen deprivation is a crucial cause of injury to the cortex and cerebrum in severely unwell individuals [55].

6.3. Clinical presentations of cerebellar infection.

Studies and case reports have shown that injuries due to COVID-19 infection of the cerebellum can include ataxia, dizziness, headache and vertigo [57]. Specific symptoms, such as irregular rapid alternating hand movements, head titubation, wide-based and ataxic gait, impaired tandem gait, and mild truncal swaying while sitting on a bed were reported [57]. The scale for the assessment and rating of ataxia (SARA) score for the patient in this case study was 14 out of 40, indicating the presence of severe cerebellitis. By the end of 14 days of antiviral drug therapy, the patient demonstrated a significant remission of vertigo, and his SARA score was improved to 9 out of 40; after one month, his ataxia remarkably improved, and his SARA score fell to 3 out of 40 [57]. Another study on children with COVID-19 pediatric multisystem inflammatory syndrome has reported neurological symptoms, including encephalopathy, headache, dysarthria, dysphagia, meningitis, and cerebellar ataxia [58]. Rodriguez-Quiroga et al. [56] presented five cases of ataxia-myoclonus-syndrome (AMS) during the acute phase of a mild COVID-19 infection [59]. The delayed neurological manifestation following COVID-19 infection was characteristic of most described cases, suggesting a postinfectious immunomodulatory mechanism [60]. One unknown is the underlying pathophysiology associated with neurological problems in COVID-19 individuals. Various processes are hypothesized, including direct viral damage, the influence of cytokine

production, hypoxia, neuroinflammation, and endothelial dysfunction [61]. There is also a theory that a post- or para-infective immune-facilitated etiology causes AMS [62], whereby antibodies attack cerebellar Purkinje cells [63].

In the research by Werner et al., the patient appeared with the cerebellar syndrome, slightly scanning speech, and limb-, truncal-, and gait ataxia upon admission 16 days after the beginning of COVID-19 respiratory disease and 1 day after the remission of COVID-19 upper respiratory symptoms. They reported a case of cerebellar syndrome, with other aspects normal [64]. In the research by Ciolac et al. a patient's neurological condition was evaluated, which indicated bilateral limb ataxia, with the left limbs being more severely affected, bulbar palsy (mostly dysphonia and dysphagia), a diminished gag reflex, and the absence of nystagmus. The patient's cerebellar and bulbar syndromes gradually recovered over the following two weeks, whereas cognitive and behavioral impairment continued. Cognitive impairment was distinguished by diminished visuospatial skills, linguistic fluency, and focus. Behavioral impairment was marked by periods of abrupt yelling, chest-beating, poor judgment and insight, and lack of restraint (i.e., inappropriate naked body postures, urinating in the room, etc.). The neuropsychological evaluation revealed modest cognitive impairment (23 on the Montreal Cognitive Assessment), moderate depression (19 on the Beck Depression Inventory), and minimal anxiety (Hamilton Anxiety Rating Scale score: 9) [45].

In the research by Grimaldi et al. [62], COVID-19 was identified in a 72-year-old male. The neurologic examination revealed a cerebellar syndrome (dysarthria, ataxia, action tremor, and upper-limb dysmetria) accompanied by widespread spontaneous myoclonus predominantly affecting the proximal limbs, increasing with movement, and also being stimulus-sensitive. The remainder of the neurologic evaluation revealed typical results, including ocular motility and deep tendon reflexes.

6.4. Histopathological methods show severe damage.

COVID-19 affects the function and morphology of many organs and body tissues, including lungs, kidneys, heart, liver, and brain [65]. Several studies have reported hypoxic alterations and neuronal loss in the hippocampus, cerebral cortex, and cerebellar Purkinje cell layer, despite no signs of major thrombi or acute stroke [66-69]. However, some studies reported atherosclerosis and microhemorrhages in brain specimens [69-71]. Other histopathological findings include progressed myelin loss, terminal hypoxic-ischemic injury typified by necrotic neurons in the hippocampus and cerebellum, perivascular cellular infiltrates, with differing levels of axonal damage being observed [67,69]. The study of Bryce et al. [68] reported that only one patient showed signs of a remarkably large cerebral artery territory infarct, and three patients demonstrated minor and sparse peripheral

and deep parenchymal ischemic infarcts, while others were hemorrhagic. In addition to these microhemorrhages, some vascular congestion that worsens vascular damage and reperfusion injury has been reported [69,70].

7. Blood vessel abnormalities in the cerebellum of COVID-19 patients.

7.1. Stroke leads to severe cerebellar damage in COVID-19

In some cases, neuroinvasion of coronavirus is very severe and leads to stroke, especially cerebellar stroke [72]. COVID-19 infection increases hypoxia, inflammatory hyper-response, and distributed intravascular coagulation, which are triggers for the induction of stroke. Cerebellar infarction and damage to the brainstem, in addition to other factors, can cause sudden death in critically ill COVID-19 patients [72,73]. In patients with minor symptoms of COVID-19, ischemic stroke and extensive carotid strokes can be seen; such effects may be caused by a 'cytokine storm' triggered by the disease. Alterations based on the patient's bleeding score have constrained the use of anticoagulants and likely explained stroke relapse and low efficacy of anticoagulants in patients [74].

7.2. Cerebellar hemorrhage; an adverse effect of COVID-19

Cerebral hemorrhage has been seen in a small number of COVID-19 patients. CT scans have uncovered a left basal ganglia hemorrhage in one case [75]. CT scans have demonstrated large right-side cerebellar and interventricular hemorrhage [76]. Post-mortem dissection, showed cerebellar hemorrhage and intense infarcts within the dorsal pons and medulla; strikingly, microglial nodules and neuronophagia within the inferior olives and multifocally within the cerebellar dentate nuclei were reported [76].

In one Patient with COVID-19, CT showed intra-axial cerebellar hemorrhage causing cerebellar edema that subsequently resulted in brain death [38].

7.3. Cerebellar microbleed; a relationship with cognitive impairment?

Patients with SARS-COV-2 disease can show ischemic stroke or lethal intracerebral hemorrhage. Autopsies have indicated micro thrombosis and acute cerebellar hemorrhagic infarcts in many COVID-19 patients [77].

The notion of critical illness-related microbleeds has been recognized [78]. In the study by Kirschenbaum et al. [75], all patients investigated experienced hypertensive microangiopathy and hypertension; however, hypertensive microbleeds also profoundly damaged infratentorial and deep

grey matter regions [77]. Cerebral microbleeds have been related to an increased probability of cognitive deterioration and cardiovascular mortality [77].

8. Autoimmune reactions in the cerebellum due to COVID-19

8.1. Cerebellitis and ataxia; all ages at risk.

Acute cerebellitis is an inflammatory condition characterized by cerebellar edema and dysfunction, which is considered to be caused by infection (most often viral) and, less frequently, immunization [79,80]. Patients with acute cerebellar impairment (ataxia, nystagmus, or dysmetria), headache, nausea, and altered consciousness are common manifestations. It is an uncommon disorder with several clinical manifestations. Acute cerebellitis should be suspected whenever symptoms indicative of posterior fossa involvement is present. Although occurrences of acute cerebellitis are more prevalent in youngsters, the condition should also be considered in adults [81,82].

A report of a rare case of post-COVID-19 acute cerebellitis in a 24-year-old male is presented [83].

In terms of COVID-19-related neurological symptoms, dizziness and diminished awareness are among the most common. Nevertheless, less common neurological complications such as seizures, Guillain-Barré syndrome, and ataxia may also occur [64]. A case report has detailed that a 62-year-old man developed subacute cerebellar disorder with ataxia of the limbs and trunk after the clinical reduction of the symptomatic SARS-CoV-2 [64]. This study suggested that SARS-CoV-2 infection may cause postinfectious neurological complications. These neurologic symptoms have not been reported broadly without related respiratory symptoms, but have been found in the aged.

8.2. Autoantibody associated cerebellitis; the role of anti-GAD antibody.

Emekli et al. [78] reported a further case study whereby although a SARS-COV-2 RT-PCR test was negative, the anti-GAD antibody was identified with a high titer and within a range associated with the etiological cause of cerebellitis. This patient had other comorbid immune system disorders, including autoimmune gluten sensitivity and thyroiditis. It was proposed that there is a coordinated pathogenetic relationship between SARS-CoV-2 disease and anti-GAD-associated autoimmune cerebellitis [84]. A further case study reported that COVID-19 led to the development of Bickerstaff Brainstem Encephalitis (BBE) [85]. Moreover, several other autoimmune neurological conditions, including Guillain-Barré disorder, Miller Fisher disorder, acute necrotizing encephalitis, myelitis, intense dispersed encephalomyelitis (ADEM), and myasthenia gravis have been detailed after COVID-19 [86].

A further case study identified an autoimmune antibody positive patient with SARS-CoV-2 encephalitis and ataxia [87]. Although nasopharyngeal RT-PCR was negative, cerebrospinal fluid CSF analysis showed the presence of SARS-CoV-2. Although immunotherapies are utilized to treat postinfectious immune-mediated conditions, they may decrease the patient's antiviral immune function and compromise CNS infection [87]; this possibility should be further explored.

9. Conclusions

The worldwide COVID-19 pandemic is widely reported to affect vital organs including the respiratory system and some parts of the CNS. Interestingly, MRI, PET, and CT scans of infected people have pointed to cerebellar damage. ACE2 facilitates the viral entrance to the cerebellum as evidenced by the presence of SARS-COV-2 RNA in the cerebellum, and the presence of ataxia, a disease intimately associated with cerebellar dysfunction. Cerebellar infection decreases the patient quality of life. Manifestations including stroke, hemorrhage, and microbleeds have been observed in cases showing cerebellar infection, and autoimmune reactions within the brain stem and cerebellar have also been seen in COVID-19 cases, implicating a role of different parts of the immune system in an abnormal reaction towards the cerebellum, resulting from misdirected responses (Figure 1). Taken together, we believe the cerebellum, a critical contributor to correct brain function, is susceptible to attack from the SARS COV-2 virus, the possible result of which is a wide range of neurological symptoms from ataxia to stroke mediated by different damaging mechanisms (e.g., inducing autoimmune reactions, inducing blood clots and hemorrhage, and direct infection of neural and glial cells in the cerebellum). We propose that more comprehensive research projects are urgently required to elucidate the basic and molecular mechanisms of cerebellar damage due to COVID-19.

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Figure legend:

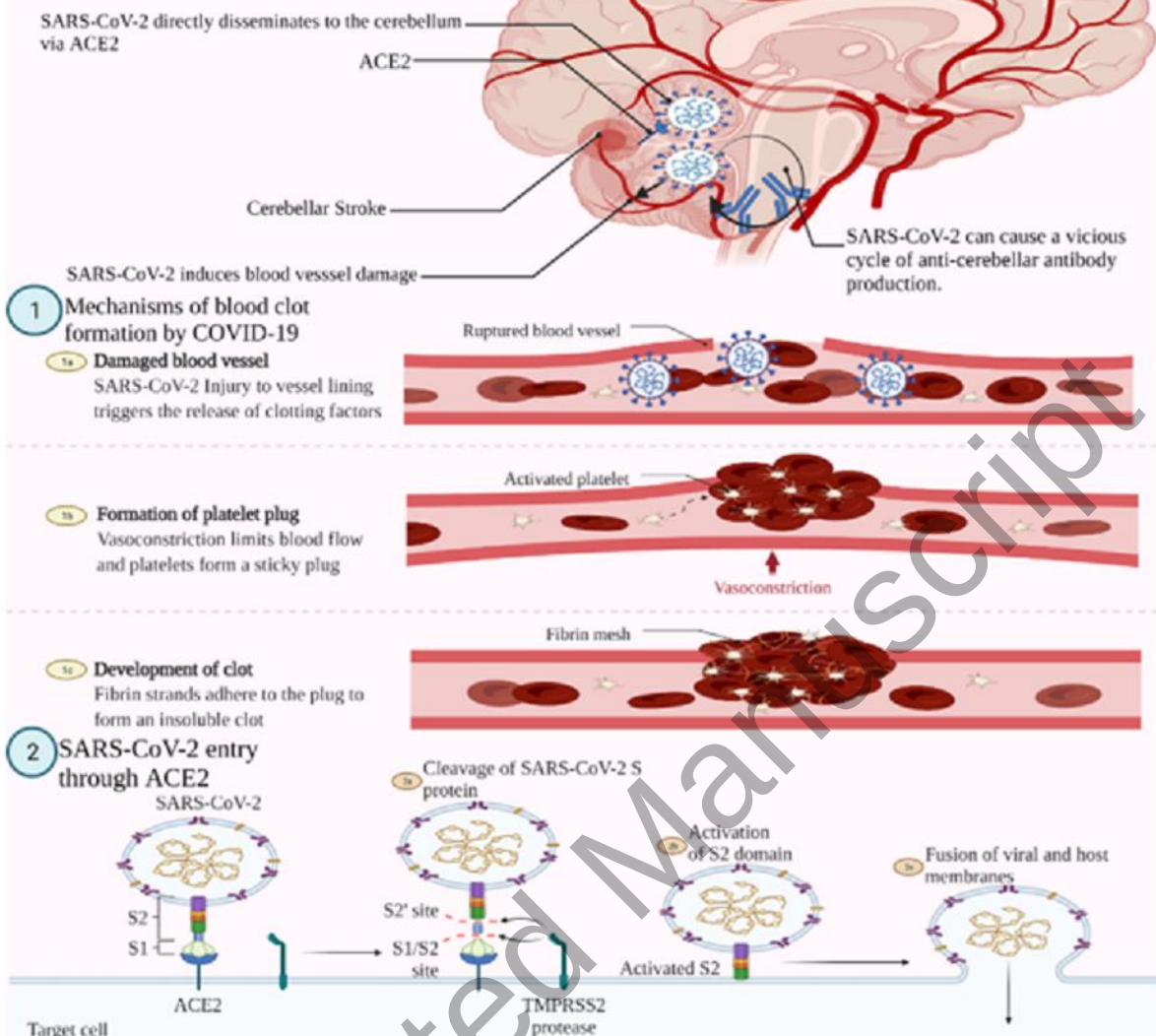
Fig.1 Mechanisms of COVID-19 induced cerebellar damage.

There are various mechanisms by which SARS-CoV-2 can damage the cerebellum, such as, autoimmune anti-cerebellar antibody production, directly invading the cerebellum through the ACE2 receptor, and causing stroke by inducing endothelial vascular damage in cerebellar arteries. 1. SARS-CoV-2 induces blood clot in three steps; 1a. Damaging cell lining, 1b. platelet aggregation, 1c. fibrin formation. 2. SARS-CoV-2 enters the cerebellar cells via ACE2 in three steps; 2a. S protein cleavage, 2b. S2 domain activation, 2c. membrane fusion of host and virus. Created with BioRender.com

Abbreviations: *ACE2*: angiotensin converting enzyme 2, *COVID-19*: Coronavirus disease 2019, *S*: spike protein, *SARS-CoV-2*: severe acute respiratory syndrome coronavirus 2, *TMPRSS2*: transmembrane serine protease 2

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Mechanisms of cerebellitis induced by COVID-19



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Table 1: Cerebellar involvement in COVID-19 via the lens of clinical studies

Method of detection	Finding	Outcome	Reference
MRI	Cerebellar stroke	-	[88]
CT	Cerebellar stroke	Patient was neurologically stable in follow up	[89]
CT and MRI	Acute ischemic stroke in cerebellar vermis	Patient completely recovered	[90]
CT and MRI	Cerebellar stroke	Patient expired	[91]
CT	Cerebrovascular accident in the cerebellar artery that caused ischemic stroke	Patient recovered	[92]
MRI	Multiple acute ischemic areas in both cerebellar hemispheres and vermis	Patient discharged from hospital	[47]
CT	disperse low attenuation of the cerebellar hemispheres causing concern for diffuse anoxic damage possibly related to posterior circulation restriction	—	[72]
Autopsy	Cerebellar hemorrhage	Patient died	[76]
CT and CTA	Hemorrhages and infarcts of cerebellar hemispheres	One Patient expired and one Patient remained in icu	[38]
MRI	cerebellar syndrome with limb-, truncal- and gait ataxia and scanning speech	Patient recovered	[64]
MRI and lumbar puncture	ACPA	Patient recovered	[93]
MRI	Anti-GAD-associated autoimmune cerebellitis	—	[84]

CT, PET, MRI, and autoantibo dy testing	Subacute cerebellar syndrome	Patient recovered	[94]
CT, MRI	Acute brainstem and cerebellar dysfunction	Patient recovered	[86]

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