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Review article

The neurological insights of the emerging coronaviruses

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ABSTRACT

Emerging Viral diseases are incredibly infectious and proficient in inducing pandemics. Unlike the previous emerging coronaviruses (ECoVs) which neurological complexities were uncommon, with neurological features exhibition at 14–25 days post-onset, yet with critical outcomes exhibiting >50% mortality in central nervous (CNS) presenting pathologies. The COVID 19 neurological consequences occur more frequently even in mild cases, presenting with CNS involvement in up to 25%, musculoskeletal and peripheral manifestation (PNM). Through preceding ECoVs case reports, the PNM not linked to fatal outcomes, however, required, repeated neuro-imaging as notable CT and MRI changes appeared as late as 21 days while the likelihood of Cerebrospinal fluid to test positive for ECoV was 25%, only in the CNS presenting cases. Owing to 44–60% myalgia presentation, risk of the high inflammatory state, and coagulation cascade abnormalities reported in ECoVs, testing for C-reactive protein, serum creatine kinase, and D-dimer level is mandatory. Presently, there is no antiviral medication or vaccination for the ECoVs, early induction of antiviral drugs remains the backbone of management. Neurologically, the therapeutic dosages of anticoagulants are linked to the high incidence of thrombotic complexities, while methylprednisolone is associated with myopathy. Future studies expected to apply more neuro-imaging techniques for CNS exploration and further explore the pathogenesis of the COVID 19 myalgia, anosmia/ageusia reported in the majority of the initial cases.

1. Introduction

The emergence of an infectious disorder usually involves multiple factors, for instance, vectors' ecological remodelings, microorganisms genomic material mutation, weather modification, natural calamities, and anti-microbial usage [1]. Furthermore, emerging viruses (EV) appear when individuals traverse new boundaries and become jeopardized to infection, EV transmitted to humans from distinct species where they happened to be typically benign. Further, the mammalian host often is an intermediate transmission agent [2]. Additionally, EV diseases are extraordinarily infectious and proficient of inducing epidemics as evidenced by outbreaks of Filoviruses (Ebola and Marburg) virus in 1967 and 1976 respectively, Paramyxoviruses (Hendra and Nipah) virus 1994 and 1998 sequentially, and CoV: coronaviruses (SARS-CoV: severe acute respiratory syndrome, MERS-CoV: Middle East Respiratory Syndrome, and SARS-CoV-2) in 2003, 2012 and 2019 successively [2–7].

The coronaviruses (CoVs) were recognized 60 years ago and are associated with human and diverse animal infections. They acquired the name due to unique presentation of virions under electron microscopy, which manifests a fringe of extensive, bulbous covering prominences forming a model implicative of the solar corona. Further, CoVs considered clinically inconsequential until the emerging of SARS-CoV, MERS-CoV, and the most recent COVID-19. However, family Coronaviridae in which CoVs apply, befall in the order Nidovirales, which extra redivided into three genera, namely alpha, beta, and gamma; moreover, CoVs are single-strand RNA genome of relatively 30 kb, enveloped, round, with a diameter of approximately 120 nm [8,9]. To date, 7 CoVs have been shown to infect humans. The normal human CoVs Betacoronavirus HCoV-OC43 and HCoV-HKU1, as well as Alphacoronavirus HCoV-229E, causative agents of common colds in pediatrics and geriatrics and Alphacoronavirus HCoV-NL63 the causative agent of pediatrics bronchiolitis, furthermore, for the past 18 years, 3 emerging CoVs (ECoVs), the Betacoronavirus affecting animals have emerged and provoked epidemics in humans, namely, SARS CoV in 2002 (in the subgenus Sarbecovirus), and MERS-CoV in 2012 (under the subgenus Merbecovirus) and SARS-CoV-2, subfamily *Orthocoronavirinae,* under the subgenus

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Sarbecovirus (Beta-CoV lineage B) [3,10,11]. These 3 ECoVs will form the core of the review of this article.

Moreover, unlike other RNA viruses, the unpredictability towards host varieties and pathogenicity of the ECoVs is owing to their capability to undergo mutation and recombination when various strains infect the related cells and proffer origin to a novel viruses [12].

Even though CoVs commonly recognized for inducing respiratory ailments, both clinical and experimental research types have illustrated their solid tropism towards the neurological system, with inherent neuropathological outcomes in genetically or susceptible cases, with or without supplementary environmental outrages. The evidence supporting pathogenesis is still unclear, hence understanding the mechanisms and the outcomes of CoV interactions with the neurological system is fundamental to appreciate likely pathological outgrowths fully [8,13]. However, there is actual proof that human respiratory CoVs can manifest with extra respiratory manifestations, including neuroinvasive features; indeed, SARS-CoV, the OC43 CoV, and 229E CoV detected in the brain tissues of autopsied SARS cases and multiple sclerosis cases [12,14]. Similarly, reported a new neurological manifestation among the COVID-19 confirmed cases [15].

Unlike respiratory presentations of ECoVs, which are well investigated, there is tiny existing knowledge on the neurologic presentations [16]. Hence, the knowledge of the novel ECoVs symptoms and case reporting need be advanced, aiming at creation of the infection control models and venture clinical trials for therapies advancements [17]. In such circumstances, this article is meant to contribute the understandings of the neurological manifestations of the ECoVs traversing the aspects of the epidermiologial data, clinical presentation, diagnostic considerations and the potential pharmacological options.

2. Epidemiology

Numerous viruses can contaminate the mammalian central nervous system (CNS), some with overwhelming outcomes, others ending with chronic infections [18]. The mortality of encephalitis secondary to viral infections extends from 4 to 29%, and approximately 50% of survivors are at a considerable risk of acquiring neurological complications. Nevertheless, in one of the comprehensive analysis study involving 183 hospitalized pediatrics cases presenting with CNS and acute respiratory tract infection (ARI), CoV infection observed in 12.02% of the cases presenting with CNS involvement, majority of the cases had fever followed by headache and vomiting [19].

It is apparent that infection by the SARS virus not restricted to the lungs, but also exhibits systemic complications, as evidenced by 65 cases with hallmark of SARS lymphocyte destruction; further, extensive propagation of the SARS virus into cerebral neurons demonstrated from the 8 SARS confirmed cases based on the autopsy studies [20].

MERS-CoV neurological symptoms are likely to present in 1 out of every 5 MERS-CoV cases before or after the viral confirmation [21]. In one of the first retrospective studies assessing the intensive care unit (ICU) MERS-CoV cases, severe neurological syndrome with fluctuating rates of altered consciousness, ataxia, localized motor disturbances, and hyperintense lesions bilaterally was observed among MERS-CoV confirmed cases [22]. Nevertheless, the resulting small retrospective research showed more than 25% of MERS cases to present with confusion and more than 8% with seizure presentation [23]. Neurological pathologies secondary to MERS treatment abundantly observed [24]. Similar to SARS-CoV, the MERS-CoV infection exhibits systemic complications, and CNS involvement appears to be another target [21].

In the first COVID-19 comprehensive report on neurologic exhibitions among the in-patients, up to 1/3 cases found to present with neurological consequences, yet the study recorded the cases from one city, advanced neuroimaging and invasive diagnostic schemes were evaded mostly due to the risk of cross-infection [15].

Further, the major neurological hallmarks of the SARS-CoV-2 observed in three classes, CNS manifestations comprising confusion, dizziness, cephalgia, impaired consciousness, convulsion, critical cerebrovascular pathologies, and ataxia. In contrast, neuropathic pain, gustatory/olfaction dysfunctions, and ophthalmic pathologies affect peripheral and musculoskeletal systems [15,25].

Populationally (Table1), during the SARS-CoV outbreak in China 2002–2003 about 8096 cases were affected, approximately 90% of cases recovered and >700 deaths globally with the majority of the death due to comorbidities such as diabetes (DM), cardiac pathologies (CAP), or a weak body immunity with principally case fatality ratio of 10% [5,20,26]. In comparison to adults, pediatric cases manifested with less severe complications, low incidence, and rarely transmitted SARS-CoV; meanwhile, the large numbers of healthcare workers (HCW) suffered a severe strike by SARS [27].

Comparatively, during MERS-CoV outbreak in Arabian Peninsula (2012), >2000 cases were recorded globally over the past five years, with >40% severe cases or deaths, and >50% of the deaths reported in those with the underlying medical conditions like DM, CAP, hypertension (HTN) or chronic renal failure (CRF), meanwhile, the case fatality rate was approximately 35% [5,28–30]. Likewise, about 98% of MERS-CoV cases were noted in adults, predominantly in males in approximately 65–68.5% with the median age of 52 years, concurrently, nearly 17% of the HCW reported with SARS-CoV infection [31,32].

In the most contemporary ECoV pandemic, the COVID-19, notwithstanding meticulous quarantine attempts globally, the rate of COVID-19 advances, with >4,000,000 laboratory-confirmed victims and over >300,000 global deaths [33].

Table 1
The overview of the emerging corona viruses.

		SARS-CoV	MERS-CoV	SARS-CoV-2	REF
1	Epicentre	Guangdong Province (2002)	Arabian Peninsula (2012)	Global Pandemic	[5–7,33]
2	Nomenclature	Betacoronavirus, subgenus Sarbecovirus	Betacoronavirus, subgenus Merbecovirus	*Betacoronavirus*, subgenus *Sarbecovirus* Beta-CoV lineage B	[3,10,11]
3	Reservoir	Bat, Palm civets	Bat, Camels	Bat, Snakes	[37,38]
4	Population Affected	8096	>2000	>4,000,000	[5,20,26,28–30,33]
5	Incubation	2–13 days	2–14 days	2–12 days	[5,31]
6	Transmission	Animal to human, human to human	Animal to human, human to human	Animal to human, human to human	[5,34]
7	Multi-systemic complications	YES	YES	YES	[34,35,37]
8	Neurological complications	YES	YES	YES	[15,20,21]

ABBREVIATION: CoV-Corona Virus, REF-References

The most of the infected cases appear to be men in up to 73%, with 32% of the case with comorbidities, mainly DM, HTN, and cardiac diseases and the average of 49 years, meanwhile 98% of cases presented with pyrexia, other symptoms incorporated cough, myalgia, headache, hemoptysis, and diarrhea [34,35].

Aetiologically, SARS-CoV, in which the epicenter was in Guangdong province, is linked to bats as the reservoir. The contemporary theory is that the SARS coronavirus arose from bats from which it infected diverse intermediate mammalians. Furthermore, this transformation to dissimilar hosts needed the CoV to bear mutation for humans then acquired the virus; nonetheless, the virus looks to have needed additional mutation in the spike protein genes to allow active replication in humans to create additional human to human deliverance [2,9,36].

Whilst, MERS-CoV linked to the one-humped camels (dromedary camels) as the reservoir and the principal source of human MERS-CoV infections [9,36]. Additionally, up-to-date findings have confirmed bats to be also the significant reservoirs of MERS-CoV [37]. Human to human transmission, expressly in healthcare contexts, has been the central route of transmission in numerous cases. The mean incubation duration is between 2 and 14 days [31].

Meanwhile, the genetic code analysis revealed the SARS-CoV-2 to be most closely related to 2 bat SARS-like coronavirus samples, similar to MERS-CoV and SARS-CoV; there is evidence of mutation before infecting people; additionally, comprehensive bioinformatics scrutiny implied probability of SARS-CoV-2 to have arisen from snakes. Nonetheless, evidence of human to human transmission published [34,38,39].

3. Clinical presentation

3.1. General clinical presentation

While earlier ECoVs neurological complexities did not appear to arise simultaneously with respiratory manifestations, instead exhibited delay by 14–21 days, in the COVID-19, most neurologic manifestations occur as early as the first two days; further, neurologic symptoms emerging as an important differential diagnosis for COVID-19 [15,21]. Considering that, the neurologist must familiarise themself with general ECoV manifesting symptoms and signs rather than concentrating on neurological manifestation only.

The clinical standards for SARS diagnosis require the presence of a history of pyrexia, or documented pyrexia $\geq$38 °C, and the presence of 1 or more other symptoms of lower lungs (cough, troubled breathing, shortness of breathing) and radiographic proof of lung infiltrates compatible with pneumonia and non-existence of alternative diagnosis that can thoroughly describe the disease [40]. The initial chest CT usually displays patchy consolidation originating with a single peripheral lesion that advances to multiplied lesions or ground glass presentation. Meanwhile, on full blood picture (FBP), lymphopenia often remarked and advances during the illness; seldom, thrombocytopenia and prolonged APTT identified, nonetheless, raised LDH levels is poor outcome prediction [41].

By contrast, MERS begins with pyrexia, cough, pharyngitis, muscle aches, and joints pain, succeeded by dyspnoea, and fast progress to pneumonia in 7 days, frequently warrants ventilatory assistance [42]. Abnormal chest X-rays are more prevalent than in SARS cases, with up to 89% of cases requiring ICU care, unlike SARS, the clinical pattern of MERS is more severe in immunocompromised cases and regularly mild in patients with no comorbidities [14,43]. Additionally, up to 72% of MERS patients likely to manifest with comorbidities [44]. Correspondingly, RT-PCR is warranted for MERS-CoV confirmation and ruling out differentials like H1N1 and Influenza A and B [36,45].

On the contrary, regarding detection, the N-Gene of MERS-Coronavirus, the most contemporary study, has established the proof that (RT-LAMP-VF) a nucleic acid imagery method that incorporates the reverse transcription loop-mediated isothermal amplification method and a vertical flow visualization strip (RT-LAMP-VF) to be better than real-time RT-PCR (rRT-PCR) [46].

Further, similarities of clinical features (pyrexia, cough dry in nature, dyspnoea, and ground-glass opacities on chest CT scans in up to 98% two-sided entanglement) between SARS-CoV-2 and preceding ECoV infections noted. However, few cases with SARS-CoV-2 an infection had striking upper respiratory tract signs and symptoms and infrequently exhibited GIT manifestations compared to the previous ECoV cases. Moreover, IFN-γ-inducible protein 10, Monocyte chemoattractant protein 1, MIP1A, and TNFα presence rises as a predisposing factor for ICU admission [34,47]. Then as well, cases that attain the case definition for suspected COVID-19 require a screening priority for the SARS-CoV-2 with RT-PCR [48,49].

3.2. Neurological presentation

3.2.1. The central nervous system manifestation

Critical acute neurologic pathologies infrequently characterize ECoV; in one study, status epilepticus (SE) has shown to be the manifesto of the entrance of SARS CoV within the Cerebrospinal fluid (CSF). Further, SE is recognized to be a seizure lasting for 5–30 min or longer without annulling automatically, or either as seizures repeatedly reappearing with no full consciousness restoration amid succeeding events. In one case, five days post-admission in 59 years lady, SE presented with reappearing seizures not responding to phenytoin treatment and extended episodes up to 30 min accompanied with confusion. RT-PCR repeated twice tested positive for both CSF and serum specimen, while the CSF viral load was 6884 copies/mL and serum viral load was 6750 copies/mL. Besides, chances of metabolic disarrangements, renal failure, stroke, cranial trauma, and hypoxia excluded [16,50].

Similarly, SARS CoV entry into the CSF during pregnancy might present with generalized seizure, as a rule, excluding eclampsia by noting blood pressure and proteinuria is mandatory. Moreover, ruling out the likelihood of drug toxicity (Ribavirin), acute renal failure (ARF), Acid-base changes, and CNS infection obliged. In the inadequacy of contraindications, a lumbar puncture is necessary whereby CSF RT-PCR, opening pressure, clearance, protein, glucose, stain, and cultures necessitate recording; additionally, Electroencephalogram and MRI are mandatory [51].

SARS-CoV-2 CNS manifestation befalls in approximately 25% of the cases. Further, the recent onset of seizures reported as a manifestation of SARS-CoV-2 encephalitis and meningitis. They are associated with confusion and loss of consciousness and meningeal irritation signs, while MRI revealed hyperintensities lesions. Further, there are reports on the diagnosis confirmation by positive CSF RT-PCR rather than a nasopharyngeal swab [52–55].

Acute cerebrovascular accident (CVA) is not unusual in critically ill cases with multiple co-morbidity. On the contrary, large vessel cerebral infarctions (LVCI) are rare among SARS cases, but when present outcomes are critical with the increased fatality rate (Table 2). In one prospective study involving 5 cases, LVCI showed high susceptibility to thromboembolic episodes, with up to 1/3 of the critically ill cases ended up with deep vein thrombosis and hypercoagulable state [56,57].

Moreover, in trying to rule out possibilities of CNS ECoV manifestation, repeated MRI checkup is mandatory. In a retrospective study involving ICU MERS-CoV cases, the initial CT of the 74 years man with comorbidities (DM, HTN, and dyslipidemia) revealed no acute changes rather than multiple chronic small vessels (lacunar) strokes. Surprisingly the MRI repeated three weeks later had

Table 2
The central nervous system manifestation of the emerging corona viruses (SARS/MERS).

Case	Author/Year	Age/sex	Neurological Diagnosis	Supportive lab results	Imaging	Comorbidities	Status
1.	Hung, 2003	45/F	Status epilepticus	Serum+VE/CSF +VE SARS-CoV	CT: Normal	RND, fungal peritonitis	A
2.	Lau, 2004	32/F	Generalized seizure	Serum+VE/CSF +VE SARS-CoV	Normal MRI, EEG	Pregnancy	A
3.	Umapathi, 2004	68/F	LVCI	Serum+VE SARS-CoV	Brain CT: Infarction	no vascular risk factors	A
4		64/F	LVCI	Serum+VE SARS-CoV	Brain CT: MCA infarction	no stroke risk factors	D
5		54/F	LVCI	Serum+VE/SARS-CoV	Brain CT PCA and MCA	Dyslipidaemia and hyperthyroidism	D
6		63/M	LVCI	Serum+VE/CSF −VE SARS-CoV	Brain CT: infarction	DM, HTN, IHD	A
7		39/M	Right occipital lobe Infartion (Autopsy)	Serum+VE/CSF −VE SARS-CoV	–	no stroke risk factors	D
8	Arabi, 2015	74/M	Acute disseminated encephalomyelitis	Serum+VE/CSF −VE MERS-CoV ↑protein	MRI T2/FLAIR: hyperdense lesions	DM, HTN and dyslipidemia	D
9		57/M	Vasculopathy	Serum+VE MERS-CoV CSF -No	CT: patchy hypodense lesions	DM, HTN	D
10		45/M	Encephalitis	Serum+VE/CSF −VE MERS-CoV ↑protein	MRI T2/FLAIR: hyperdense lesions	DM, HTN, PAD	A
11	Al-Hameed, 2017	42/F	Spontaneous ICH	Serum+VE MERS-CoV	CT: SAH	RND, DM	D

ABBREVIATION: LVC – large vessel cerebral infarctions, ICH Intracranial Hemorrhage, +VE – Positive, -VE – Negative, CSF – Cerebrospinal fluid, RND – Renal Disease, DM – Diabetes mellitus, HTN – Hypertension, PAD – peripheral artery disease, Hypertension, IHD – Ischemic hart disease, A – Alive, D – Dead

remarkable findings of various bilateral patchy regions of signal anomaly that appeared high on T2/ FLAIR images observed in the peri-ventricular, deep white matter, subcortical region. The observation implied an acute disseminated encephalomyelitis (ADEM). Of note, this case presented with high-grade fever, altered mental level, with ataxia and focal motor deficits. Ended up into coma and died 30 days post-admission, importantly, CSF protein and leucocyte are usually raised in ADEM. However, negative CSF MERS-CoV RT-PCR rose another diagnostic challenge in these cases [22,58].

In the first COVID-19 CVAs case-based series, identified that CVA symptoms occurred in the early stages of illness with co-occurring comorbidities. Further, the association with high inflammatory state and abnormalities with coagulation cascade thought as CRP: C-reactive protein and D-dimer titers detected raised [59].

On general physical examination of ECoV cases, a neurologist must observe if the patient is obese and confirm by measuring Body mass index. This is especially so when dealing with confirmed or suspected MERS cases, as the DPP4 enzyme implicated in glucose metabolism is displayed in large amounts in obese people compared with non-obese people. Nevertheless, it is the port of entry of MERS-CoV into human cells. In one case report involving an obese 42-year with multiple comorbidities, ended with spontaneous intraventricular hemorrhage [60].

3.2.2. The peripheral nervous system manifestation

Peripheral nerve dysfunctions regularly induced by dysfunction of the peripheral motor, sensory, or autonomic nerves. Similar to CNS ECoV related disorders, peripheral nervous system (PNS) disorders does not coincide with the onset of SARS; instead, symptoms tend to appear 21–25 days later. Further, neuromuscular disorders (NMD) in these cases observed to fall under critical-illness polyneuropathy (CIP), myopathy (CIM), or both. Amongst the cases exhibited polyneuropathy, the NCSs revealed decreased CMAP amplitudes. Never the less, diminishing of nerve conduction velocity, temporal dispersion or conduction block, does not appear to be the peculiarity of SARS-NMD. On the other side, the EMG explicated acute denervation. Of note, large doses of intravenous corticosteroid treatment may generate acute steroid myopathy [57,61].

Further, regarding myopathy and rhabdomyolysis, a pair of commonly suggested mechanisms are direct muscle invasion by ECoV particles and immune-mediated muscle injury, satisfactory proof of the direct invasion of SARS CoV into the muscle cells is still lacking [57,62]. In one postmortem skeletal muscle research based on 8 SARS cases, the diagnosis of critical illness myopathy (CIM) was verified based on clinical features; namely, generalized flaccid paresis, linked risk factors, raised serum creatine kinase, and histological features. Besides, the nonexistence of myofiber atrophy in subjects with no steroid treatment proposes the contribution of steroid as the essential agent in the CIM mechanism [63,64].

The viral-induced myositis proposed owing to the abundance cases manifesting with myalgia and a raised serum CK level. In one cohort research encompassed SARS cases, ascertained that more than 60% of the cases presented with myalgia and muscular disturbance on the initial consultation, a different study reported 30% of the SARS cases had raised serum CK levels with myopathy exhibiting with significant myofiber atrophy particularly for cases in whom hydrocortisone administered. Never the less, in a most recent prospective case analysis of the SARS-CoV-2 confirmed cases, 44% myalgia or fatigue reported; future studies expected to explore whether this is a feature of viral effected myositis like previous ECoV [34,63,64].

Despite of neuromusculoskeletal sequelae, SARS victims endured periodic relief of pain and weakness recovery following conservative management and resumed daily activities [65]. CIM and neuropathy are underdiagnosed pathologies in the ICU contexts and propose notable morbidity and mortality rates; diagnosis proposed when a critically ill case presents with limb weakness or ventilator dependence with no cardiac or pulmonary pathologies. In a case series report involving 4 confirmed MERS-CoV, a 43-year lady, who neurologically displayed initial severe myalgia among other general symptoms without any comorbidities, ended up with ICU care, neurological testing revealed symmetrical lower limb weakness, with intact sensations, mildly decreased deep tendon reflex bilaterally, importantly, in such cases, it is mandatory to

exclude other NMD within the neural axis with similar features, namely, Guillain Barre syndrome, botulinum toxin susceptibility, continuing neuromuscular blockade, and Lambert-Eaton myasthenic syndrome [21,66].

Furthermore, olfactory neuropathy has reported as a rare form of typical peripheral neuropathy induced by SARS-CoV. When dealing with cases of ECoV physicians must asses the CN I critically, it is mandatory for the physician to exclude possibilities of olfactory bulb trauma from history taking, olfactory glioma, frontal lobe meningioma, a lesion in the sub frontal region, nasal cavities and paranasal sinuses by MRI. Moreover, neurodegenerative disorders, and Parkinson's disease, which typically affect CN 1 before cognitive and motor manifestations, never the less clinical judgment and otolaryngological consultation are necessitated as anosmia is much more frequently due to the common cold and local causes in the nasal cavity [67,68].

Anosmia and ageusia befall in >80% among COVID-19 cases, either as a first presentation or as the only neurological sign in mild cases [69]. Guillain Barré syndrome (GBS) accompanied by COVID-19 may cause PNS quandary, even ere respiratory manifestations resolve, principally displaying fast-evolving quadriplegia, raised protein level, and moderate leukocytosis yet negative CSF RT-PCR stated [70,71].

The COVID 19 Miller Fisher syndrome (MFS) symptoms preceded by infection and presented with ageusia, bilateral abducent nerve palsy, areflexia, and albuminocytologic dissociation, Moreover the interface between MFS and GBS, the polyneuritis cranialis have been reported proposing a para/postviral consequences [72].

3.2.3. The central and peripheral nervous system co-existence manifestation

There is evidence that ECoV neurological symptoms may overlap as in Bickerstaff's encephalitis (BBE) overlapping with GBS in MERS cases, it is important to note, BBE cases who acquire limb weakness diagnosed as having an overlap with GBS, yet, BBE, together with MFS and GBS thought to set a perpetual clinical spectrum [21,73]. Mimics require exclusion with the aid of clinical history, cerebral MRI, and CSF conclusions whereby CSF albuminocytologic dissociation and the appearance of antiganglioside antibodies and may aid BBE confirmation [21,74].

4. Pharmacological options

Presently, there is neither vaccine nor antiviral medication for human and zoological CoV [75]. The backbone management remains the induction of antiviral drugs as soon as possible following illness encounters. Nevertheless, prescription choices for SARS-CoV involved Ribavirin, a nucleoside analog with the significant drawback of lacking necessary in-vitro action against ECoV and with the significant side effect being hemolysis in several cases. Further, a boosted protease inhibitor regimen, lopinavir-ritonavir (LPV/r) have anti-CoV action in vitro, and IFN- alpha is a broad-spectrum antiviral medicine [37]. Similarly, there is no availability of precise or accredited MERS CoV human vaccines; besides, numerous CoV vaccines are at various developmental stages targeting both humans and dromedary camels [36,76].

Similar to the SARS-CoV outbreak, therapeutic options such as ribavirin, interferons, and corticosteroids shown tiny to no clinical usefulness, notwithstanding efficacy exhibition in nonhuman primates [76]. The ongoing multicenter, randomized controlled trial, the MIRACLE (MERS-CoV Infection treated with A Combination of LPV/r and intErferon-β1b) trial targeting the result of 3 months fatality expected to come with conclusive investigations on the effectiveness of blend therapy of LPV/r and recombinant IF-β1b [77].

Overall, there are no certain antiviral medications or vaccines for SARS-CoV-2, options based on the background of managing SARS-CoV, MERS-CoV, or novel influenza virus. In addition to the previously mentioned regimes, ShuFengJieDu, and Lianhuaqingwen the Chinese medication, Remdesivir, and Oral oseltamivir offer the best potential choices. However, the efficiency and safety still need to be verified by clinical experiments; importantly, for SARS-CoV-2, according to the guidelines, IFN- alpha and LPV/r are recommended as antiviral therapy [75].

Neurologically, SARS-CoV, and COVID-19 cases presented with seizures managed by propofol, phenytoin, and Levetiracetam. Valproate and midazolam also employed in addition to antibiotics hydroxychloroquine or antiviral [16,51–54]. Similarly, a five days intravenous immunoglobulin dosage have been employed among COVID-19 GBS patients, but no significant therapeutic benefit in improving GBS symptoms reported [70,71].

In managing critical ECoV cases with LVCI, the therapeutic dosages of low molecular weight heparin (LMWH) confirmed linked to a high frequency of thrombotic complexities in up to 1/3 of the cases [56]. Furthermore, nasal spray steroids and oral cobalamin prescribed in the management of acute CN I inflammation, yet anosmia endured during follow-up to more than 48 months. In one case report in which a triple antiviral therapy regimen incorporating subcutaneous pegylated interferon alpha-2a, high-dose oral ribavirin, and oral LPV/r, sensory symptoms seemed to recover over 6–7 months steadily [21,78].

Owing to the vast number of cytokines provoked by SARS, MERS, and SARS-CoV-2, corticosteroids were used regularly for critical case management, aiming to reduce the inflammation and influence pulmonary damage. Still, contemporary data in SARS and MERS cases implies no benefit of corticosteroid on mortality rather than prolonged viral clearing [16]. Intravenous methylprednisolone has been used supportively in ECoV neurological cases [60]. Massive intravenous corticosteroid dosages may influence CIM. Hence, to limit CIM, avoiding corticosteroid treatment is recommended [57,79].

5. Conclusion

Unlike SARS and MERS pandemics where neurological complications were uncommon, yet presented with critical outcomes, in COVID 19 pandemic, the neurological symptoms reported frequently even in mild cases. Through case reports, the mortality rate of the SARS and MERS cases exhibited central nervous manifestation was (6/11) 54.5% with accompanied comorbidities in (8/11) 72%, while those with peripheral manifestation were not likely to present with fatal outcomes. Comparatively, 25% of the COVID 19 neurological quandaries befall in CNS complications.

The neuroinvasive features in the preceding ECoVs did not coincide with ECoVs onset, instead, delayed by14-25 days and centrally present as generalized seizure, Status epilepticus, Ischemic, and hemorrhagic stroke, vasculopathy, spontaneous ICH and ADEM. Meanwhile, peripherally manifest as CIP, CIM, BBE overlapping with GBS, ICU acquired GBS and CN I neuropathy, and obesity is a significant risk factor. Furthermore, it is mandatory to repeat imaging as significant CT, and MRI changes appear as late as 21 days in some cases more marked at T2/FLAIR in MRI. The SARS-CoV-2 neurological consequences occurred as early as the first two days or as the only presenting symptoms, manifesting with CNS, PNS, or musculoskeletal.

On lab examination, the focus should be on serum creatine kinase level as 44–60% of ECoV cases presents with myalgia, while the likelihood of CSF to test positive for ECoV(2/8) 25% only in the CNS presenting cases. Never the less, D-dimer and CRP warrants monitoring.

Presently, there is no vaccination nor antiviral therapy for the ECoV, early induction of antiviral drugs remains the backbone management, neurologically the therapeutic dosages of LMWH are linked high frequency of thrombotic complexities while methylprednisolone is associated with myopathy. Future inter-continental studies, exploring prognosis, outcomes and applying neuroimaging techniques expected to explore the SARS-CoV-2 neurological implications fully.

Conflicts of interest/disclosures

The authors acknowledge that they have no financial or other conflicts of interest regarding the publication of this research.

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