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### The coronavirus family neurological effects: A literature review

Abdulwahab Alahmari

Radiology Specialist, Radiology Department, Saudi Arabia

**\*Corresponding Author:** Abdulwahab Alahmari, Radiology Specialist, Radiology Department, Al-Namas General Hospital, Ministry of Health, Al-Namas City, Saudi Arabia, Tel: +966562428716; Email: [afaa99@hotmail.co.uk](mailto:afaa99@hotmail.co.uk)

**ORCID ID:** <http://orcid.org/0000-0002-9959-830X>

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#### Abstract

All the lethal coronaviruses like the middle east respiratory syndrome, severe acute respiratory syndrome coronavirus, or the new coronavirus have showed similar and non-similar effects on the central nerves system. The aim of this paper is to summarize the published findings as neurological effects of the most dangerous three viruses in the coronavirus family and to find the common neuropathological patterns among the three viruses.

**Keywords:** Brain; MERS-CoV; SARS-CoV; SARS-CoV-2; Neurological effect; Coronavirus

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#### Literature review

The aim of this literature review is to study the neurological effects caused by the middle east respiratory syndrome (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and the new coronavirus known as COVID-19 or (SARS-CoV-2). As well, Finding the common and uncommon patterns of neurological effects among the three of most lethal viruses in the coronavirus family is the focus of this paper.

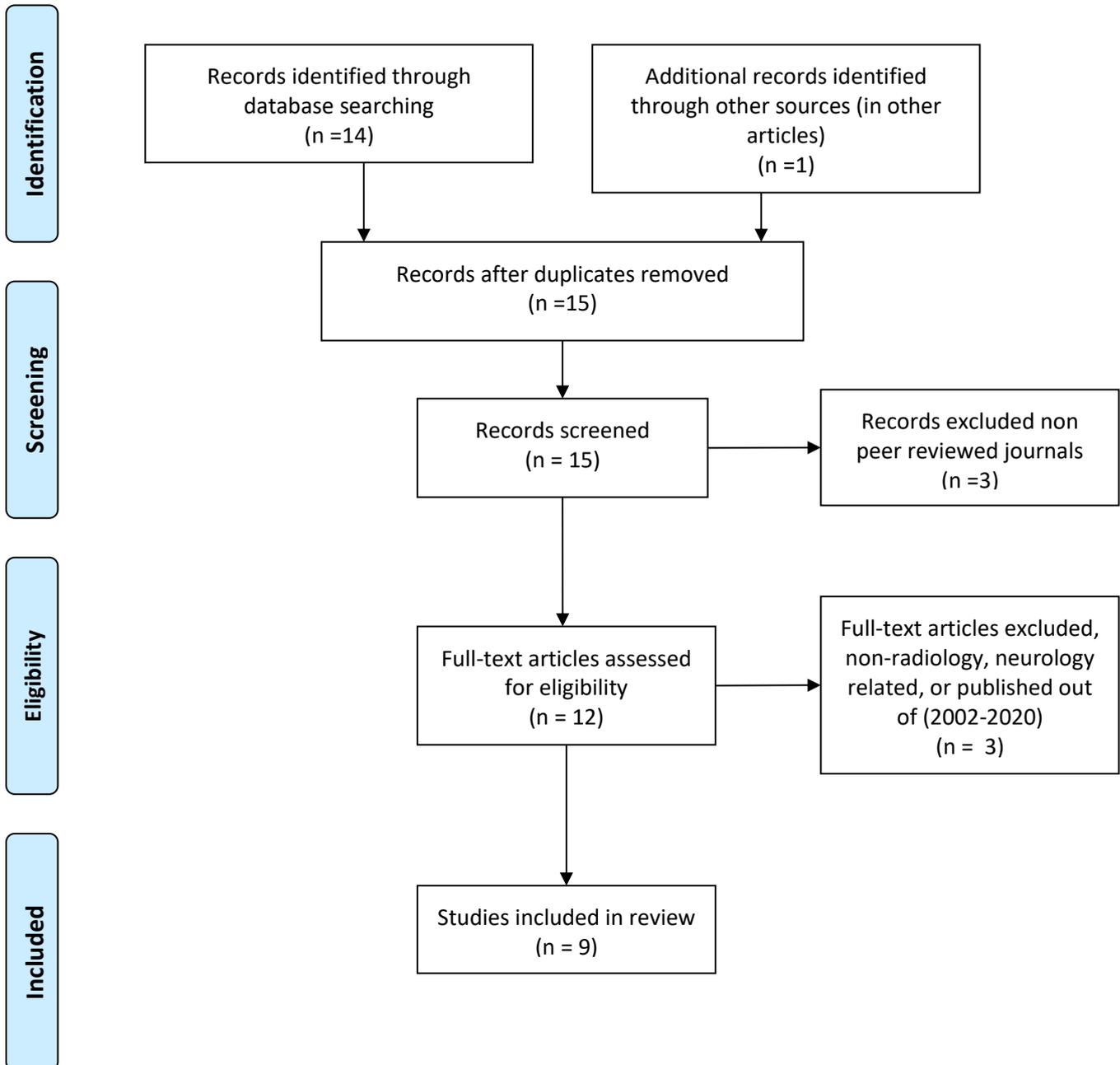
#### Methodology

A Google Scholar engine search for the terms “MERS-CoV, SARS-CoV, SARS-CoV-2” combined with the term “neurological effect” was done to find the relevant papers. The search

with the previous terms started in April 5<sup>th</sup> 2020 and ended in April 16<sup>th</sup> 2020. Any paper published in a peer reviewed journal from 16<sup>th</sup> November 2002 (since SARS-CoV started) to 16<sup>th</sup> April 2020 (this paper deadline) were collected. Any paper has no radiological or neurological contribution was excluded see (Figure 1).

#### Introduction

The most lethal viruses in the coronavirus family (i.e. MERS-CoV, SARS-CoV, SARS-CoV-2) showed different effects on the nervous system ranging from mild to life-threatening conditions. The following is an overview of these neurological effects:



**Figure 1:** A PRISMA diagram for the selection process.

### Medullary cardiopulmonary centers in the brainstem

Probably the most difficult symptom on the coronavirus patient is not the fever, but it's the

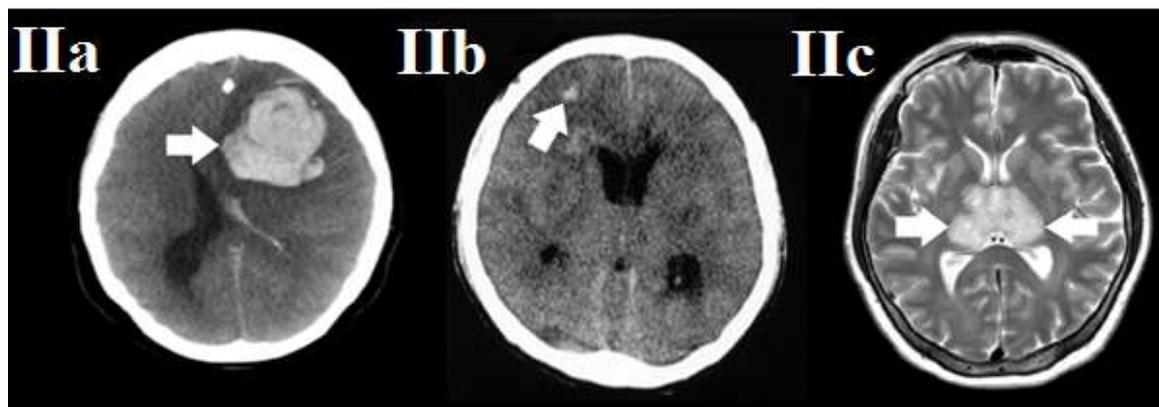
short breath (respiratory distress). Some of the patients required ventilators, so they can breathe. The lethal coronaviruses are usually associated with pneumonia which makes the breathing very difficult. But it has been proved that SARS-CoV passes through

chemoreceptors and mechanoreceptors of the lungs from one neuron to another neuron to attack the medullary cardiopulmonary centers in the brainstem through synaptic connections [1]. The breathing becomes more difficult due to the infection in the brainstem. Similarly, SARS-CoV-2 could be transmitted to the brainstem through synaptic connections similar to SARS-CoV [1].

### Intracranial hemorrhage

MERS-CoV can cause platelet dysfunction, thrombocytopenia, and disseminated

intravenous coagulation which leads to prolonged coagulation profile then will cause a multi-organ failure then irreversible brainstem damage which eventually will lead to death. Polyneuropathy has been reported as non-direct consequences of the MERS-CoV [2]. The brain damage in SARS-CoV case due to hyper-dense lesions has been proven see (Figure 2). There is a SARS-CoV-2 case with thalamic hemorrhage which is a common finding in among the lethal viruses of the coronavirus family see (Figure 2).



**Figure 2:** Three medical imaging study of three patients. The patient (A) is 34-year-old female patient with brain hemorrhage (a confirmed case of MERS-COV disease). The patient (B) is 50-year-old female patient with diffuse brain edema and multiple hyper densities lesions suggestive of ischemic and necrotic changes (a confirmed case of SARS-COV disease). The patient (C) is 50 year old female patient with bilateral thalamic hemorrhage (a confirmed case of SARS-COV-2 disease). Findings: The patient (A) study is axial CT scan for the brain show left intracranial hemorrhage, inter-ventricular extension, midline shift, and brain edema (white arrow). The patient (B) study is axial CT scan show multiple hyper-densities -in different slices located upper and lower than the showed slice, but has the same features of the presented scan- with diffuse brain edema (white arrow). The patient (C) study is axial T2 MRI scan show bilateral thalamic hemorrhage that

was confirmed as hypo-intense susceptibility weighted images (white arrow). Technique: (A) axial CT, cerebrum window. (B) axial CT, cerebrum window. (C) axial MRI, T2.

### Long term neurological sequelae

It has been proven that SARS-CoV mostly enter the brain through the olfactory bulb leading to neurons death. The infection was detected in the brain mostly attacking the cardiopulmonary centers in the brainstem, while a minimal infection presented in the lungs [3].

### Extent of the infection in the brain parts

MERS-CoV affect the corticospinal tract, ventricles (causing inter-ventricular hemorrhage), subcortical, basal ganglia, corpus callosum, temporal lobe, parietal lobe, and frontal lobe by different lesions. As well,

SARS-CoV affect the olfactory bulb, cerebrum, and cardiopulmonary centers in the brainstem. Similarly, SARS-CoV-2 affect the brainstem, thalamus, olfactory bulb, and cerebrum, while the cerebellum remains as the uninfected part of the brain by SARS-CoV-2 [3].

### **Acute necrotizing encephalopathy (cytokine storm syndrome)**

There is a confirmed case of SARS-CoV-2 of a woman with bilateral thalamic and temporal lobe damage on both CT and MRI scans [4]. The findings are bilateral medial temporal lobe and thalamic bleedings on FLAIR and they were confirmed by susceptibility weighted images [4]. These findings are similar to another published case of influenza A virus subtype H3 with a fatal acute necrotic encephalitis [5]. The disruption of blood-brain barrier is associated with cytokine release which causes the bleeding.

### **Symptoms & neurological presentations in coronavirus family**

The common patient presentations of MERS-CoV are; low mental functions, headache, seizures, dizziness, limb numbness, and nausea [2]. The common patient presentations of SARS-CoV are; low mental functions, headache, and vomiting<sup>3</sup>. The common patient presentations of SARS-CoV-2 are; low mental functions, headache, vomiting, and anosmia & ageusia (olfactory and taste disorders (OTDs)) [4,6].

### **Hyperthermia vs. brain**

The normal body temperature is 37.7 °C (99.9 °F) and any temperature beyond 40 °C can be life-threatening temperature. The developing brain is at risk from hyperthermia. As well, the developed brain can have some effects which depends on the degree of the temperature and the duration of the exposure. In case of a severe hyperthermia, it could induce neuronal necrotic death. Even with lower temperatures, hyperthermia-induced damage can cause neurons to show a late apoptotic characteristic.

The mechanism of hyperthermia-induced damage is done by depolarizing the mitochondria in the neurons which would lead to cell damage [7].

### **Low oxygen saturation vs. brain**

The normal oxygen level in the blood is 75 to 100 mm HG and if the oxygen level dropped below 60 mm HG, the patient will need a ventilator. The decrease in oxygen level in the blood will lead to a hypoxia. Brain hypoxia can be categorizing into 4 categories; diffuse cerebral hypoxia, focal cerebral ischemia, massive cerebral infarction, and global cerebral hypoxia. Similar to the body temperature, the low oxygen saturation effect on the nervous system has two important factors; the amount of oxygen in the blood and the period of shortage. The categories of hypoxia are associated with the previously mentioned two factors. The world health organization report claim that the mean incubation time for SARS-CoV-2 is 5.2 days based on a study among 425 patients in Wuhan and it may widely vary among patients which depends on their immune systems [8]. Another paper claims that the SARS-CoV-2 incubation period is 6.4 days [9]. If a patient have a low oxygen saturation for a long time, it could lead to white matter periventricular lesions, infarctions, or cognitive impairments. It is similar to chronic obstructive pulmonary diseases (COPD). The COPD patients with low oxygen saturation, they could develop white matter periventricular and subcortical lesions which will lead to cognitive impairments and mental illness [10].

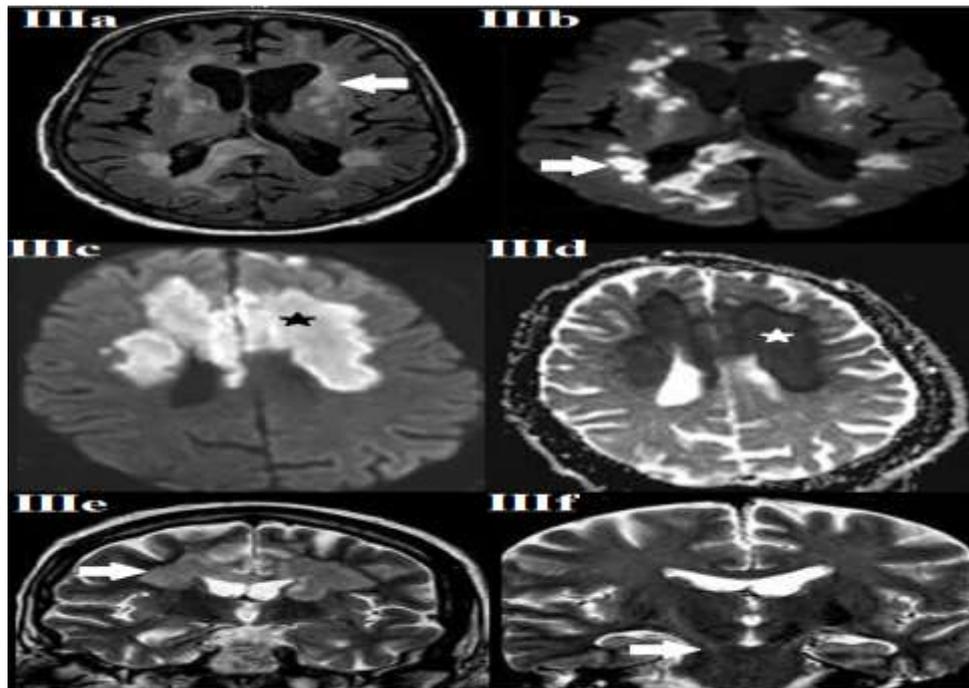
### **Meningitis and encephalitis**

One SARS-CoV-2 case was reported to be associated with Meningitis and encephalitis [11]. In the report, the patient brought to the hospital due to convulsion and loss of consciousness not because of fever or respiratory issues. The patient's MRI scan revealed ventricular hyper-intensities on DWI, partially atrophied hippocampus, high signal intensity in the temporal lobe and hippocampus on FLAIR, and pan sinusitis on T2 [11].

### White matter lesions

MERS-CoV can cause lesions in the white matter in different regions like; subcortical, basal ganglia, corpus callosum, temporal lobe,

parietal lobe, and frontal lobe see (Figure 3). The white matter lesions will cause ataxia, focal motor deficit, and coma [12]. All the brain lesions in the MERS-CoV patient did not show any gadolinium enhancement on MRI [12].

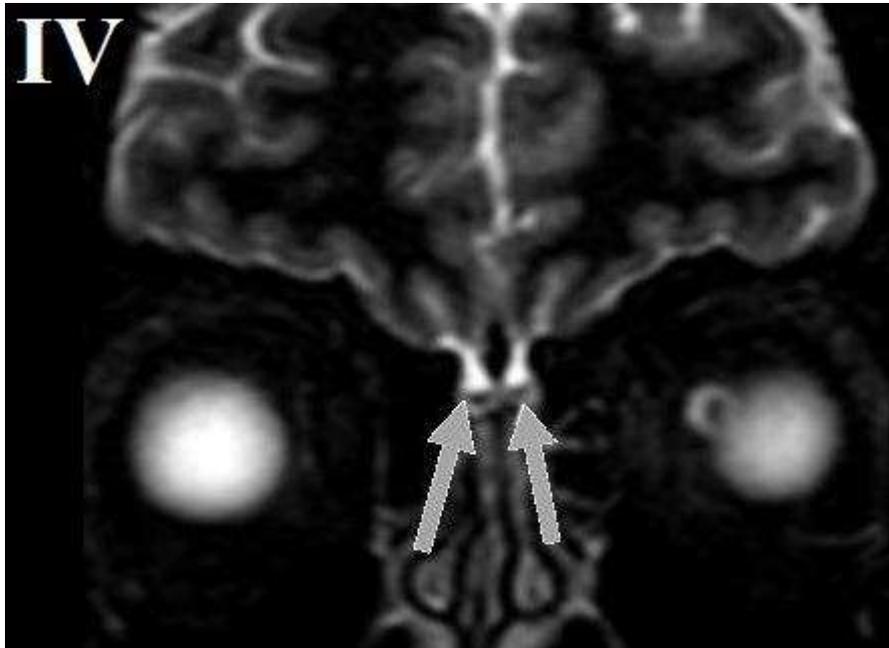


**Figure 3:** Both MRI scans on top (3a and 3b) for a 74-year-old male patient show multiple bilateral subcortical white matter lesions. The MRI scans (3c, 3d, and 3f) for a 57-year-old male patient show bilateral subcortical white lesions. The MRI scan (3g) for a 45-year-old male patient shows corticospinal tract abnormality (all are confirmed MERS-CoV). Findings: The FLAIR image (3a) shows multiple hyper-intense lesions in the corpus callosum and in the deep white matter and subcortical lesions bilaterally in the frontal, temporal, parietal lobes (white arrow). The DWI image (3b) shows multiple white matter lesions (white arrow). The DWI and ADC images (3c and 3d) show diffusion restriction of the corpus callosum and bilaterally in the frontal lobe (black and white stars respectively). The T2 image (3f) shows bilateral hyper-intense white matter lesions in the corpus callosum and frontal lobe (white arrow). The T2 weighted image (3g) shows abnormality affecting the corticospinal tract bilaterally (white arrow). Technique: (3a) axial MRI, FLAIR image. (3b and 3c) axial MRI, DWI image. (3d) axial MRI, ADC image. (3f) coronal MRI, T2 image. (3g) coronal MRI, T2 weighted image.

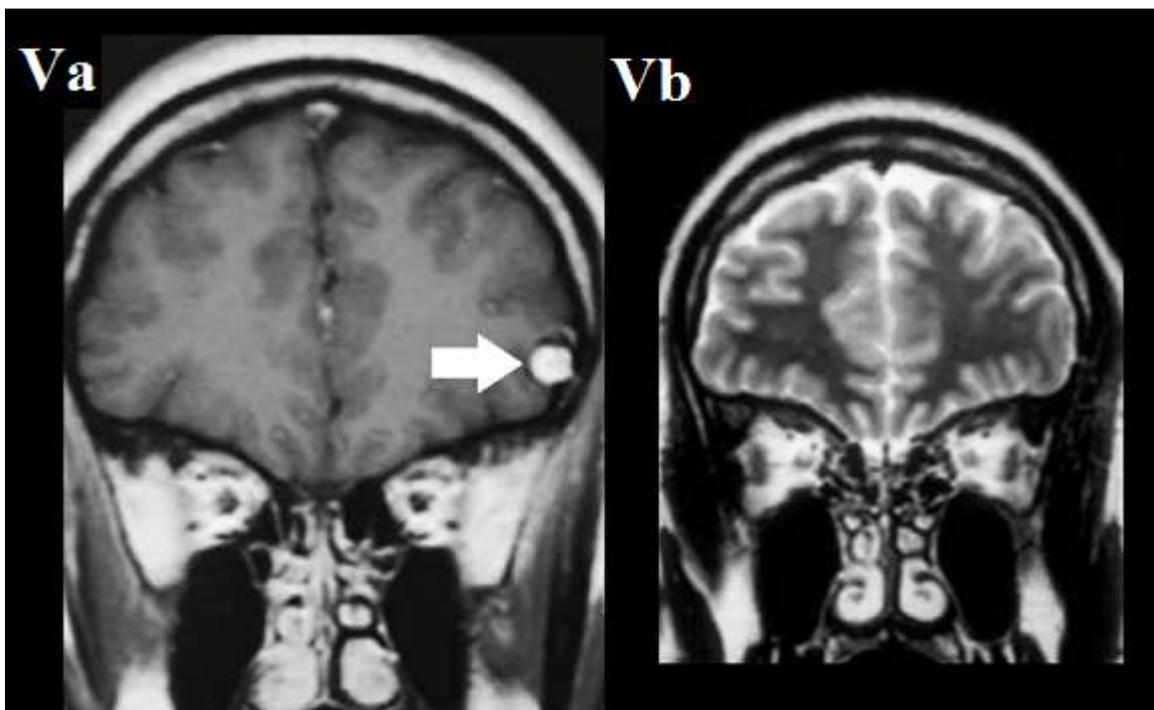
### Olfactory nerve

It has been proven that the olfactory nerve is affected by SARS-CoV-2 in acute stages with no nasal congestion [13]. In such cases, the MRI images will show a high signal intensity in the olfactory bulb see (Figure 4). As well, anosmia and olfactory neuropathy was reported in SARS-CoV with no abnormal

MRI finding in the olfactory bulb<sup>14</sup>, but a temporal epidermoid cyst was found in the scan see (Figure 5).



**Figure 4:** A 27 year-old-male patient with ansomnia and olfactory bulb neuropathy (a SARS-CoV-2 confirmed case). Findings: A T2 wighted image, coronal slice, MRI scan shows a normal volume, no nasal congestion, and olfactory bulb signal intensity (grey arrows). Technique: Coronal MRI, T2 wighted image.



**Figure 5:** A 27-year-old female patient with insomnia and temporal epidermoid cyst. Findings: A coronal T1 MRI image (5a) shows a temporal epidermoid cyst on the left side. A coronal T2 MRI image (5b) shows no abnormal findings in the olfactory bulb (white arrow). Technique: (5a) coronal MRI, T1 weighted image. (5b) coronal MRI, T2 weighted image.

### Lack of post-mortem investigation

There is a reporting shortage in the literature in post-mortem cases by medical imaging and autopsy for the coronavirus cases due to infection control reasons. This lack causes a huge misunderstanding of these viruses and very minimal knowledge of their mechanisms in the central nervous system [1]. As well, due to the focus on the respiratory system, there is a neglect and lack of papers that help in documenting the various effects that is caused by the lethal coronaviruses on the nervous system. Even though, SARS-CoV and MERS-CoV started in 2002 and in 2012 respectively, but still there is a lack of information see (Table 1).

**Table 1:** The published papers about neurological effect of the coronavirus family supported by radiology scans.

Author	Publishing Year	Journal	Article Type	Neurological Findings
Li YC et al.	2019	Journal of medical virology	Review	Medullary cardiopulmonary centers affected by SARS-CoV-2 which cause death.
Algahtani H, et al.	2016	Case reports in neurological medicine	Case report and review of the literature	MERS-CoV cause brainstem irreversible damage then death.
Netland J, et al.	2008	Journal of virology	Animal experimental study	SARS-CoV enter the brain through the olfactory nerve then attack the cardiopulmonary centers in the midbrain.
Poyiadji N, et al.	2020	Radiology	Case report	SARS-CoV-2 cause acute necrotizing encephalopathy
Hjelmsæth J, et al.	2020	Tidsskrift for Den norske legeforening	Case report	SARS-CoV-2 cause loss of smell and taste
Moriguchi T, et al.	2020	International Journal of Infectious Diseases	Case report	SARS-CoV-2 cause Meningitis/Encephalitis
Arabi YM, et al.	2015	Infection	Case report	MERS-CoV affected the white matter
Galougahi MK, et al.	2020	Academic radiology	Case report	Confirm olfactory bulb neuropathy in SARS-CoV-2 on MRI.
Hwang C.	2006	Acta Neurologica Taiwanica	Case report	Can't confirm the olfactory bulb neuropathy on MRI in SARS-CoV with temporal lobe findings.

## Conclusion

Coronaviruses have a huge effect that is targeting the central nervous system which leads to other symptoms like; vomiting, anosmia, ageusia, respiratory distress, etc. The real issue is happening in the brainstem more than the lungs or the gastrointestinal system which is primarily led to death in some vulnerable cases with chronic conditions. Medical imaging investigation of the central nervous system must be done like the chest CT or swab test for confirmed coronavirus cases. To tackle the issue, an MRI must be done for the confirmed cases to detect any abnormality in the brain and especially the brainstem of the corona patients. A post-mortem pan CT can help in identifying other affected systems and our understanding of these viruses' mechanisms in damaging the human body. The etiology of coronavirus family summarized see (Table 2).

**Table 2:** Etiology table.

Lethal Coronavirus Type	Confirmed Etiologies	Radiological Patterns
MERS-CoV	Intracranial hemorrhage	Intracranial hemorrhage, inter-ventricular extension, midline shift, and brain edema.
	Brainstem damage	High signal corticospinal tract extending above the brainstem.
	White matter lesions	Affect the subcortical, basal ganglia, corpus callosum, temporal lobe, parietal lobe, and frontal lobe. No gadolinium enhancement.
SARS-CoV	Intracranial hemorrhage	Multiple hyper-densities and diffuse brain edema.
	Olfactory neuropathy	N/A.
SARS-CoV-2	Intracranial hemorrhage	Bilateral thalamic and temporal lobe hemorrhages.
	Olfactory neuropathy	High signal olfactory bulb on T2 weighted images. Normal nasal volume (no congestion).
	Meningitis and encephalitis	Ventricular hyper-intensities on DWI . Partially atrophied structure like the hippocampus on FLAIR. High signal temporal lobe and hippocampus on FLAIR. Pan sinusitis on T2.
	Acute necrotizing encephalopathy (cytokine storm syndrome)	Bilateral medial temporal lobes and bilateral thalamic bleeding on FLAIR confirmed by susceptibility weighted images.

## Teaching points

There is a large similarity between the lethal viruses in the coronavirus family especially in their effects on the nervous system. The central nervous system is largely involved in the coronavirus infection and we must pay more

attention to this system which could help in saving lives.

**Abbreviations**

MERS-CoV: Middle east respiratory syndrome.

SARS-CoV: Severe acute respiratory syndrome coronavirus.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

OTDs: Olfactory and taste disorders.

COPD: Chronic obstructive pulmonary diseases.

MRI: Magnetic resonance imaging.

CT: Computed tomography.

FLAIR: Fluid attenuated inversion recovery.

DWI: Diffusion weighted imaging.

ADC: Apparent diffusion coefficient.

T1: Time 1.

T2: Time 2.

mm HG: Millimeter of mercury (pressure unit).

°C: Celsius or centigrade scale (temperature unit).

°F: Fahrenheit scale (temperature unit).

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