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A Narrative Review on the Clinical Relevance of Imaging the Circumventricular Brain Organs and Performing Their Anatomical and Histopathological Examination in Acute and Postacute COVID-19

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Abstract: Autopsy followed by histopathological examination is foundational in clinical and forensic medicine for discovering and understanding pathological changes in disease, their underlying processes, and cause of death. Imaging technology has become increasingly important for advancing clinical research and practice, given its noninvasive, in vivo and ex vivo applicability. Medical and forensic autopsy can benefit greatly from advances in imaging technology that lead toward minimally invasive, whole-brain virtual autopsy. Brain autopsy followed by histopathological examination is still the hallmark for understanding disease and a fundamental modus operandi in forensic pathology and forensic medicine, despite the fact that its practice has become progressively less frequent in medical settings. This situation is especially relevant with respect to new diseases such as COVID-19 caused by the SARS-CoV-2 virus, for which our neuroanatomical knowledge is sparse. In this narrative review, we show that *ad hoc* clinical autopsies and histopathological analyses combined with neuroimaging of the principal circumventricular organs are critical to gaining insight into the reconstruction of the pathophysiological mechanisms and the explanation of cause of death (ie, *atrium mortis*) related to the cardiovascular effects of SARS-CoV-2 infection in forensic and clinical medicine.

Key Words: acute and postacute COVID-19, circumventricular brain organs, autopsy and histopathological examination, forensic pathology and medicine, neuroimaging

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BACKGROUND

Current neuroimaging techniques provide critical insight into readily localizing and understanding the nature of brain alterations in many medical circumstances. At the same time, the need for autopsy followed by histopathology is of critical importance especially when anatomical investigation focuses on certain brain structures difficult to investigate in detail with neuroimaging given their small size and difficult localization. In this review, we address the neuroendocrine pathways associated with cardiovascular disease involving circumventricular organs (CVOs) and the paraventricular nucleus of the hypothalamus in context with clinical considerations of the CVOs and COVID-19 (coronavirus disease 2019). Given the association of the area postrema (AP) syndrome and neuromyelitis optica spectrum disorder (NMOSD) with COVID-19, we will also address the question of whether cardiovascular pathology in COVID-19 and NMOSD could be associated with circumventricular organ alteration. Furthermore, we will discuss how neuroimaging could be of relevance in detecting pathology of the AP, subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT). It has been reported that the practice of clinical autopsy followed by histopathological examination of the tissues and its integration with current neuroimaging approaches is highly relevant for forensic medicine (eg,[1–6]). This is especially applicable in the study of relatively novel diseases such as COVID-19 caused by the SARS-CoV-2 virus in both of its manifestations, acute and postacute COVID-19, for which our knowledge regarding the pathophysiological mechanisms and the explanation of cause of death are not completely elucidated.

DISCUSSION

When a new disease appears, such as during the recent COVID-19 pandemic, autopsy is the most valuable approach to understanding the disease and gaining insight on how to treat it.[7–13] At the same time, current neuroimaging methods allow us to study the human brain in clinical settings in a comprehensive, noninvasive way. That said, any neuroimaging methodology must be validated by using brain tissue as the gold standard for comparison, before that methodology can be safely applied in clinical research and practice. With respect to NMOSD and COVID-19, it follows logically that, by using combined neuroimaging and histopathological examination, the correlations of AP, SFO, OVLT, and paraventricular nucleus of the hypothalamus (PVN) neuroanatomy can be examined with imaging data.[14–16] This is an understudied area with the potential to further elucidate and increase our understanding of the neurobiological mechanisms leading to cardiovascular diseases in COVID-19 and NMOSD. It is critical to take into serious consideration the validation aspect of neuroimaging using the traditional methodology of radiological-anatomical, radiological-histological, and radiological-histopathological correlation to make imaging a valuable tool in forensic medicine enabling forensic autopsy to become minimally invasive using radiologic imaging techniques (eg,[1,6]).

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Neuroendocrine Pathways Associated With Cardiovascular Disease Involving CVOs

Three circumventricular organs, namely, the SFO, the OVLT, and the AP (eg,[17,18]) and the PVN (eg,[19,20]) are components of distinct pathways associated with the regulation of arterial blood pressure and cardiac function (Fig. 1). Specifically, they constitute a pathway leading to the secretion of vasopressin or antidiuretic hormone (ADH), given that circulating angiotensin II (Ang II) reaches the SFO and the OVLT, which in turn via axonal connections stimulate the PVN to secrete ADH (eg,[27,28]). Ang II also reaches the AP, given that the AP is characterized by high permeability of the blood-brain barrier. In another pathway critical for central autonomic regulation, the AP is involved via its structural connectivity with the nucleus tractus solitarii (NTS), the dorsal motor nucleus of the vagus (DMNV), the nucleus ambiguus, the rostral ventrolateral medulla, and the PVN (eg,[29–32]). Thus, both pathways involving the AP, SFO, OVLT, and PVN are relevant in arterial blood regulation and cardiac function; consequently, their dysfunction could well lead to cardiovascular disease (eg,[32–36]) (Figs. 1, 2).

Clinical Considerations of the Circumventricular Organs and COVID-19

Four years after the initial onset of COVID-19 and while the pandemic continues with high rates of morbidity, mortality and public health burdens worldwide (eg,[39]), there is still a remarkable paucity of data on the pathophysiology of acute and postacute or long COVID-19. Recent studies have shown that the principal effect of SARS-CoV-2 COVID-19 infection is endothelial damage and dysfunction, which extends beyond respiratory system impairment and underlies the multisystem, multiorgan clinical manifestations of COVID-19 (eg,[40–42]). Among the principal extrapulmonary targets are the cardiovascular system, the liver, the kidney, and the brain (eg,[39,43]). As elaborated upon below, it seems clear that the study of the pathways involving the AP, SFO, OVLT, and PVN is relevant not only for cardiovascular clinical research but also for SARS-CoV-2 virus infection per se. One of the reasons that the AP, SFO, OVLT, and PVN are clinically relevant in studying COVID-19 is that these brain structures show high expression of angiotensin-converting enzyme 2 (ACE2), which is a binding site of entry in the cells for SARS-CoV-2 virus (eg,[44–46]). Furthermore, the AP, SFO, and OVLT have fenestrated capillaries and are characterized by high blood-brain barrier permeability and thus are easily reachable by the SARS-CoV-2 virus via the bloodstream. Moreover, the AP has been associated clinically with the AP syndrome (characterized by intractable nausea, vomiting and hiccups for at least 48 hours) (eg,[47]), which is also one of the core clinical features of neuromyelitis optica spectrum disorder (NMOSD). Neuromyelitis optica spectrum disorder is considered an autoimmune disease in which antibodies (ie, aquaporin-4-IgG or anti-AQP4 antibodies) are produced against the water channel protein aquaporin-4 (AQP4) present in perivascular astrocytes.[48,49] AQP4 channels are present in the AP, SFO, OVLT,[50,51] and patients with the anti-AQP4 antibody show decreased levels of CSF Ang II and ACE2 reflecting severe perivascular astrocytopathy.[52] Importantly, recent reports have associated NMOSD with COVID-19, occurring after either SARS-CoV-2 infection[53] or COVID-19 vaccination.[48,54]

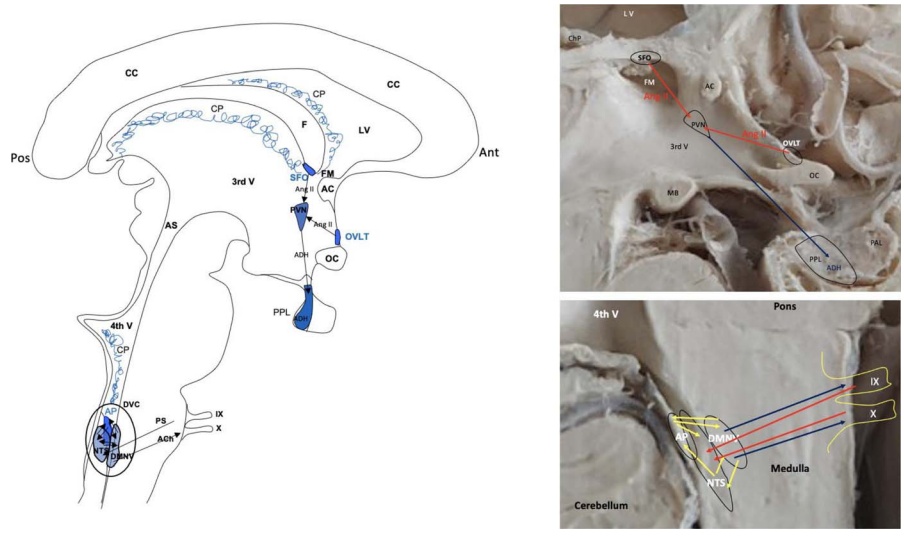

FIGURE 1. Schematic representation of AP, SFO, and OVLT neuroanatomy and their role in arterial pressure regulation. The anatomical location of the AP, SFO, and OVLT is shown in a midsagittal representation of the human brain (left) and in photographs (right). Arterial blood pressure regulation involving the hypothalamus as well as autonomic centers in the medulla can be modulated by these CVOs in 2 ways. Specifically, the SFO and OVLT affect the PVN via direct connections, which is carried out via Ang II secretion at the synaptic level. In turn, Ang II stimulates the secretion of ADH by the PVN. ADH (or vasopressin) is transported axonally to the posterior lobe of the pituitary gland (PPL) where it is released into the blood stream to produce an overall increase in arterial blood pressure by vasoconstriction and increase of blood volume.[21–25] Another mechanism of arterial blood regulation involving the CVOs is at the level of the medulla via the AP. Specifically, the AP through direct connections with the NTS and DMNV (or DVC), interconnect with the pressoceptive (PS) carotid (IXth cranial nerve), and aortic (Xth cranial nerve) bodies to modulate arterial blood pressure via a cholinergic efferent autonomic pathway.[26] AC = anterior commissure; ACh, acetylcholine; ADH, antidiuretic hormone or vasopressin; Ang II, angiotensin II; Ant, anterior; AP, area postrema; AS, aqueduct of Sylvius; CC, corpus callosum; CP, choroid plexus; DMNV, dorsal motor nucleus of the vagus; DVC, dorsal vagal complex; F, fornix; FM, foramen of Monro; LV, lateral ventricle; MB, mammillary body; NTS, nucleus tractus solitarii; OC, optic chiasm; OVLT, organum vasculosum of the lamina terminalis; Pos, posterior; PAL, pituitary anterior lobe; PPL, pituitary posterior lobe; PS, pressoceptive; PVN, paraventricular nucleus of the hypothalamus; SFO, subfornical organ; 3rd V, third ventricle; 4th V, fourth ventricle; IX, ninth cranial nerve; X, vagus nerve or tenth cranial nerve.

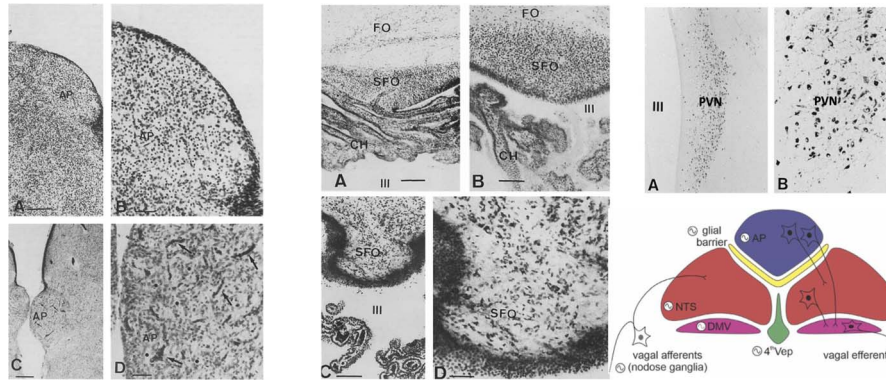

FIGURE 2. Illustration of the AP, SFO, PVN, NTS, and DMV. This figure comprises 3 columns. Left-hand column: The histology of AP is shown in four figures (A, B, C, D) (by permission from[17]). Middle column: The SFO is shown in four figures (A, B, C, D). Additional structures are indicated as follows: FO, fornix; CH, choroid plexus; III, third ventricle. Right-hand column: The upper panel (A, B) shows the PVN (by permission from[17]) at two magnifications (A, lower magnification; B, higher magnification). Please note the proximity of the PVN to the third ventricle (III) (by permission from[37]). The lower panel depicts a schematic representation of the AP and dorsal vagal complex (including the NTS and the DMV (also known as DMNV)) in the vicinity of the fourth ventricle at the axial level of the obex (by permission from[38]).

Can Cardiovascular Pathology in COVID-19 and NMOSD Be Associated With Circumventricular Organ Alteration?

Based principally on anatomical and physiological studies of the AP, SFO, and OVLT in experimental animals, there is substantial evidence regarding their role in arterial blood pressure regulation (eg,[27,38,52]). Thus, their role may be critically important in disease states, given that systolic blood pressure is strongly related to the risk of coronary and cerebrovascular events (eg,[55]). Nevertheless, to what degree and by which mechanisms the circumventricular organs are associated with arterial blood pressure and cardiovascular pathology, to our knowledge, remains unclear (eg,[32]). The SARS-CoV-2 virus shows cardiac tropism, and in COVID-19, the cardiovascular system is highly affected (eg,[56,57]). Several studies have shown that patients with preexisting cardiovascular disease affected by COVID-19 have increased mortality.[58] Generally, cardiovascular pathologies include such injuries as myocardial necrosis and myocardial edema[57] associated with cardiac dysfunction and arrhythmias[59] as well as endothelial cell injury, thrombotic events, myocarditis, myocardial interstitial fibrosis,[56] thromboembolic disease, and heart failure.[60] It is thus thought that the risk and burden of cardiovascular disease in survivors of an acute episode of COVID-19 is substantial.[60] Although these recent reports highlight the need to manage the cardiovascular complications of COVID-19, the underlying pathophysiological mechanisms are not well understood,[56,60] especially in the postacute phase of the disease.[60] Likewise, cardiovascular pathologies are frequently present in patients with NMOSD,[61] and hypertension is a major comorbidity of NMOSD.[62] However, to our knowledge, there is no literature available showing a relationship between an alteration in any of the 3 circumventricular organs discussed herein, that is, AP, SFO and OVLT, and cardiovascular disease in COVID-19 or NMOSD and hypertension in NMOSD. Given the relevance of these brain structures in arterial blood pressure regulation and their dysfunction due to AQP4 alterations in NMOSD, it seems logical to expect a contribution by these circumventricular organs to the cardiovascular disease encountered in patients affected by NMOSD. Furthermore, because NMOSD has been associated with COVID-19 after SARS-CoV-2 infection[53] or after COVID-19 vaccination,[48,54] we expect to encounter a scenario in COVID-19 patients similar to that described above for NMOSD.

Can Neuroimaging Help Us Detect SFO and OVLT Pathology?

It is in this line of clinical research that neuroimaging could be of great assistance given its noninvasive nature and its capability to be used in vivo. The diverse techniques of neuroimaging provide a tremendous wealth of information regarding the nature and location of a lesion.[63] The most popular approaches used in current clinical settings are structural T1- and T2-weighted magnetic resonance imaging (MRI) techniques, which allow us to visualize the different components of the brain at the level of gross anatomy. Depending on the clinical setting and conditions to be investigated, contrast agents such as gadolinium can be used as well. Although neuroimaging has the capability to visualize the AP, SFO, and OVLT (Fig. 3), to our knowledge, only the AP has been detected for clinical purposes to date.[65] There have been a few recent clinical reports showing alterations of the AP in patients affected by AP syndrome[47,65] and NMOSD including AP syndrome as the initial symptom.[65] Nevertheless, the latter investigation[65] did not address whether SFO or OVLT alterations were present as well. Early diagnosis of these conditions is critical for avoiding serious consequences, which can include even coma or cardiac arrest.[65] Neuroimaging could be highly useful by enabling us to identify alterations represented as hypointensities in T1-weighted images or hyperintensities in T2-weighted images at the locations of the AP, SFO, or OVLT. It should be noted that we were not able to find any publications associating COVID-19 with alterations of the AP, SFO, or OVLT. Although neuroimaging would allow us to localize an alteration in the brain, there are no techniques available to image the brain at a scale matching histological-microscopic observation.[14,15,66] Thus, a histopathological examination is necessary to gain a thorough understanding of the disease process. This can be done by biopsy or by performing autopsy followed by histopathological examination.

The Translational Power of Neuroimaging and the Importance of Clinical Validation of MRI Using Clinical Autopsy Followed by Histopathological Examination

Autopsy remains a fundamental approach in learning about human anatomy[9] and autopsy followed by histopathological examination of tissues is how we make a complete diagnosis or validation

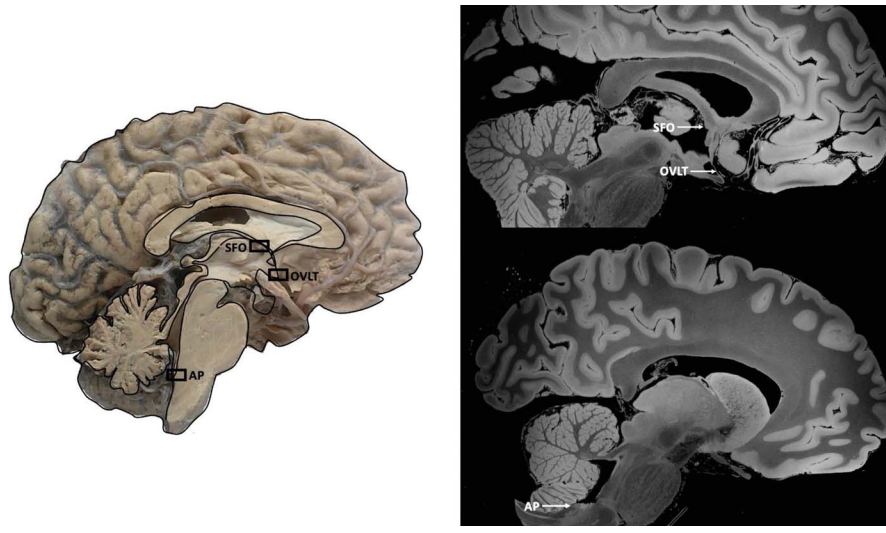

FIGURE 3. Identification of AP, SFO, and OVLT in MRI data. Current MRI enables us to visualize brain structure in detail at a macroscopic level comparable to gross anatomy. Nevertheless, clinical MRI at millimetric spatial resolution in routinely used research protocols at ultrahigh spatial resolution allow visualization of brain tissue with micrometer (μm) voxel dimensions. The right panel shows 2 sagittal sections of an ex vivo human brain obtained using MRI acquisitions with spatial resolution at 100-μm isotropic spatial resolution.[64] The left panel shows a midsagittal view of a human hemisphere with the AP, SFO, and OVLT demarcated within black rectangular areas. The AP, SFO and OVLT are also indicated by white arrows on the two MRI images of the right panel. Comparing human brain tissue with MRI images is critical to ensure accuracy in formulating anatomical interpretations in basic and clinical neuroscience using neuroimaging. Abbreviations: AP, area postrema; OVLT, organum vasculosum of the lamina terminalis; SFO, subfornical organ.

of a diagnosis, and how we gain insight into the pathological mechanisms of a disease.[10] Especially when a new disease appears, as in the recent COVID-19 pandemic, autopsy is the most valuable approach to understanding the disease and gaining insight on how to treat it. In fact, the pathologies in COVID-19 were demonstrated by histopathological examinations. Neurohistopathological studies have demonstrated acute hypoxic ischemic injury in the cerebrum and cerebellum in brain tissue of patients who have undergone autopsy (see eg,[67–72]) and characterized specific histopathological processes such as neuronal loss[67] in the frontal lobe and hippocampus as well as inflammatory alterations with activation of microglia in the medulla oblongata.[69,70] Although indispensable for a microscopic level and molecular understanding of disease processes, histopathology falls short in addressing a comprehensive examination of the brain. To attain a comprehensive and also detailed picture of the neurohistopathological process, we need to perform serial sectioning of the entire brain, which, given the cost and time requirements, is a procedure abandoned as routine since the 1980s (Dr Charles Miller Fisher, personal communication). Importantly, this aspect of clinical research can be addressed using neuroimaging that readily provides a holistic or comprehensive view of the entire brain and thus complements the classic autopsy procedure, which is "detail-oriented" (eg,[1]). Given this capability to scan the brain comprehensively, post mortem MRI has the ability to enhance autopsy and uncover otherwise undetectable findings.[3]

The Relevance of "Know-How" in Combining Imaging With Forensic Autopsy

Combining both approaches to integrate the strengths of neuroimaging in exploring the entire brain comprehensively and localizing "hot spots" for further in-depth investigation by histopathological examination, in case these brain locations are not included in the routine histopathological protocols "will open new horizons in forensic medicine and other forensic sciences, leading towards a minimally invasive virtual forensic autopsy."[1] This is part of the "know-how" in both disciplines, which is forensic autopsy and high-tech neuroimaging as stated by Thali and colleagues two decades ago[1] on how imaging can contribute and be beneficial in several forensic relevant analyses such as for visualization and pathophysiological reconstruction and explanation of the cause of death, that is, *atrium mortis*, in forensic cases. In this context, Faigle and colleagues[6] have recently developed a methodology and a tool, which facilitates MRI-histopathology correlation at the tissue level. Furthermore, as indicated by Yen and colleagues (2007), "allowing the radiological examiners to gain knowledge about forensically relevant findings and using standardized autopsy and imaging protocols as a basis for the comparison of autopsy and radiology will help to bring the two specialized disciplines closer to each other and open the door for a prolific interdisciplinary knowledge transfer."[2]

Neuroinflammation: An Example of Neuroimaging Translation in COVID-19

In a recent review article, Jonkman and colleagues (2019) highlighted the importance of neuroimaging in defining "novel MRI signatures of neuropathological lesions in neuroinflammatory and neurodegenerative disorders."[5] Given that neuroinflammatory changes are present in COVID-19, these could well be studied using an array of neuroimaging techniques. More specifically, neuroinflammation can be assessed with currently available imaging techniques such as a diffusion MRI model called the "free-water model" (see eg,[73]). Using diffusion MRI, we could localize areas of neuroinflammation to guide histopathological examination and perform correlational investigations at microscopic/ultrastructural resolution using such techniques as immunohistochemistry or electron microscopy. Furthermore, it is equally important to keep in mind that in current clinical practice, there are no imaging techniques yet available to visualize brain structure at a scale matching histological-microscopic observation. Thus, a histopathological examination remains necessary to gain a thorough understanding of the disease

process. Therefore, the combination of neuroimaging with clinical autopsy practice followed by histopathological examination will empower basic and clinical research in a useful and effective way.

CONCLUSIONS

Based on the literature reviewed herein, it follows logically that with respect to NMOSD and COVID-19 combined neuroimaging and histopathological examination can be used to examine the correlations of AP, SFO, OVLT, and PVN neuroanatomy with imaging data. This is an understudied area with the potential to further elucidate and increase our understanding of the neurobiological mechanisms leading to cardiovascular diseases in COVID-19 and NMOSD. The translation of histopathological information from the laboratory bench to the bedside has remarkable potential to advance medical innovation and especially to benefit patients and public health. Thus, the use of clinical autopsy followed by histopathological examination of tissues and its integration with current neuroimaging approaches appears to be highly relevant, and its practice should be encouraged and supported. As has been documented by several studies (eg,[1–6]), there is a need for collaboration, integration and translation among autopsy, histopathology, and radiology. "Allowing radiological examiners to gain knowledge about forensically relevant findings and using standardized autopsy and imaging protocols as a basis for the comparison of autopsy and radiology will help to bring the two specialized disciplines closer to each other and open the door for a prolific interdisciplinary knowledge transfer."[2] Overall, there is much to gain from post-mortem MRI and pathology studies, and this approach is especially relevant as new clinical questions emerge such as in COVID-19 (eg,[1–6]).

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