A Simplified Approach to Encephalitis and Its Mimics: Key Clinical Decision Points in the Setting of Specific Imaging Abnormalities

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Rationale and Objectives: Infectious encephalitis is a relatively common cause of morbidity and mortality. Treatment of infectious encephalitis with antiviral medication can be highly effective when administered promptly. Clinical mimics of encephalitis arise from a broad range of pathologic processes, including toxic, metabolic, neoplastic, autoimmune, and cardiovascular etiologies. These mimics need to be rapidly differentiated from infectious encephalitis to appropriately manage the correct etiology; however, the many overlapping signs of these various entities present a challenge to accurate diagnosis. A systematic approach that considers both the clinical manifestations and the imaging findings of infectious encephalitis and its mimics can contribute to more accurate and timely diagnosis.

Materials and Methods: Following an institutional review board approval, a health insurance portability and accountability act (HIPAA)-compliant search of our institutional imaging database (teaching files) was conducted to generate a list of adult and pediatric patients who presented between January 1, 1995 and October 10, 2013 for imaging to evaluate possible cases of encephalitis. Pertinent medical records, including clinical notes as well as surgical and pathology reports, were reviewed and correlated with imaging findings. Clinical and imaging findings were combined to generate useful flowcharts designed to assist in distinguishing infectious encephalitis from its mimics. Key imaging features were reviewed and were placed in the context of the provided flowcharts.

Results: Four flowcharts were presented based on the primary anatomic site of imaging abnormality: group 1: temporal lobe; group 2: cerebral cortex; group 3: deep gray matter; and group 4: white matter. An approach that combines features on clinical presentation was then detailed. Imaging examples were used to demonstrate similarities and key differences.

Conclusions: Early recognition of infectious encephalitis is critical, but can be quite complex due to diverse pathologies and overlapping features. Synthesis of both the clinical and imaging features of infectious encephalitis and its mimics is critical to a timely and accurate diagnosis. The use of the flowcharts presented in this article can further enable both clinicians and radiologists to more confidently differentiate encephalitis from its mimics and improve patient care.

Key Words: Encephalitis; magnetic resonance imaging.

INTRODUCTION

Infectious encephalitis is a relatively common cause of morbidity and mortality. Herpes simplex virus (HSV) alone results in an estimated 2000 deaths per year in the United States (1). Treatment of infectious encephalitis with antiviral medication can be highly effective when administered promptly. This has been most clearly demonstrated in HSV encephalitis, with antiviral medication resulting in impressive reductions in mortality (2). Despite advances in treatment, the complexity of the imaging findings and clinical symptomatology associated with infectious encephalitis can result in delays in diagnosis and treatment, and consequently poor outcomes.

Clinical mimics of encephalitis arise from a broad range of pathologic processes, including toxic, metabolic, neoplastic, autoimmune, and cardiovascular etiologies. These distinct entities need to be rapidly differentiated from infectious encephalitis to appropriately manage their separate root causes. When combined, the imaging findings and the clinical

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symptomatology of both infectious encephalitis and its associated noninfectious mimics are often unique. Thus, assessment of imaging and clinical findings *together* can frequently reveal the appropriate diagnosis, often before laboratory results are available.

MATERIALS AND METHODS

An institutional review board approval was obtained prior to initiating this health insurance portability and accountability act-compliant investigation. The requirement for subject or parent informed consent was waived by the institutional review board. A manual search of our institutional imaging database (teaching files) was conducted to generate a list of adult and pediatric patients who presented between January 1, 1995 (when the teaching file was created) and October 10, 2013 for imaging to evaluate possible cases of encephalitis and its mimics. Cases in the teaching file contain relevant clinical history such as age, sex, presenting symptoms and outcomes (surgical, pathology, or clinical follow up), and diagnostic imaging, but are otherwise de-identified. Radiology imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), was reviewed. As this was a retrospective review of teaching files, not all imaging performed on patients was available, for the purposes of review, especially in some cases with normal initial CT. Where available, pertinent medical records, including clinical notes, and surgical and pathology reports, were reviewed and final diagnoses were correlated with the imaging findings. We included adult and pediatric patients who had a final clinical or pathologic diagnosis of encephalitis or its main mimics.

The purpose of this article is to provide an intellectual framework to assess the crucial imaging and clinical decision points to facilitate the generation of an appropriate diagnosis in the setting of suspected encephalitis. Key imaging features are reviewed and are placed in the context of clinical flowcharts to simplify this often challenging diagnostic process.

RESULTS AND DISCUSSION

Group 1: Temporal Lobe Lesions

Herpes Encephalitis

Herpes simplex virus encephalitis is a substantial cause of morbidity and mortality. Infection may occur in all ages. In the absence of antiviral therapy, mortality can exceed 70% in affected individuals (2). However, prompt recognition and treatment can significantly reduce mortality, with evidence demonstrating that the early administration of acyclovir can reduce mortality to 28% (2,3). Thus, clinical recognition, laboratory analysis, and rapid appropriate imaging are paramount to the early detection and treatment.

In affected individuals, HSV-1 infection spreads via the lingual nerve to the trigeminal ganglion, where it is typically confined by the immune system, most frequently for long periods of time. Later in life, immunocompromise, stress, or trauma occasionally allow for viral reactivation. The virus overwhelms the host defense and spreads to adjacent brain structures. Headache, fever, behavioral changes, altered mental status, seizure, as well as focal or diffuse neurologic deficits may characterize the initial clinical presentation. This infectious process most frequently results in the characteristic pattern of asymmetric involvement of the bilateral limbic system, with most prominent involvement of the medial temporal lobes and less substantial involvement of the inferior aspect of the frontal lobes (4).

Polymerase chain reaction analysis of cerebrospinal fluid may be negative in the first 72 hours (5). Thus, rapid imaging is essential to disease detection and the decision to initiate treatment. CT is a relatively insensitive method of detecting early herpes simplex virus encephalitis (6). MRI provides a much more sensitive and robust analysis of imaging changes secondary to HSV (6). The widely accepted most useful clues are T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity involving the medial temporal lobe and the inferior frontal lobe, with relative sparing of the adjacent white matter (6). In more progressed cases, cortical swelling with loss of the gray-white junction may be observed. Sparing of the deep gray nuclei is typical (7). If hemorrhagic changes have occurred, these are typically apparent as areas of susceptibility artifact on gradient echo imaging. Occasionally, meningeal postcontrast enhancement is seen. In addition, diffusion-weighted imaging may assist in earlier disease detection (8).

Infarction

Brain ischemia and infectious encephalitis can share a similar acute onset. This can lead to consideration of both entities in the setting of abrupt neurologic deficits. Ischemia can be related to both arterial and venous occlusion. Ischemia secondary to anterior cerebral artery occlusion can lead to clinical signs and imaging findings related to the cingulate gyri. Although this region can be involved in herpes encephalitis, it would be atypical to be involved in isolation, as would be the case with ischemia secondary to anterior cerebral artery occlusion. Middle cerebral artery distribution ischemia may lead to temporal lobe involvement; however, the hippocampus and limbic system are typically spared. Posterior cerebral artery ischemia can lead to signal abnormality and restricted diffusion often in the occipital lobes and inferior temporal lobes, which could also be seen in various other viral encephalpathies, although a wedge-like configuration can often point to an arterial etiology. Ischemia related to venous occlusion can also mimic viral encephalitis, although the pattern of brain involvement is often characterized by distinct venous territories. Additionally, other imaging findings such as susceptibility artifact and loss of flow voids often point to a venous etiology. Although some ischemic events such as embolism can lead to bilateral areas of ischemia, these processes infrequently involve the bilateral mesial temporal lobes and limbic system in contrast to herpes encephalitis. Although restricted diffusion can be seen in herpes encephalitis, well-defined diffusion restriction