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Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement

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AIM: To assess the role of imaging in the early management of encephalitis and the agreement on findings in a well-defined cohort of suspected encephalitis cases enrolled in the Prospective Aetiological Study of Encephalitis conducted by the Health Protection Agency (now incorporated into Public Health England).

MATERIALS AND METHODS: Eighty-five CT examinations from 68 patients and 101 MRI examinations from 80 patients with suspected encephalitis were independently rated by three neuroradiologists blinded to patient and clinical details. The level of agreement on the interpretation of images was measured using the kappa statistic. The sensitivity, specificity, and negative and positive predictive values of CT and MRI for herpes simplex virus (HSV) encephalitis and acute disseminated encephalomyelitis (ADEM) were estimated.

RESULTS: The kappa value for interobserver agreement on rating the scans as normal or abnormal was good (0.65) for CT and moderate (0.59) for MRI. Agreement for HSV encephalitis was very good for CT (0.87) and MRI (0.82), but only fair for ADEM (0.32 CT; 0.31 MRI). Similarly, the overall sensitivity of imaging for HSV encephalitis was ~80% for both CT and

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MRI, whereas for ADEM it was 0% for CT and 20% for MRI. MRI specificity for HSV encephalitis between 3–10 days after symptom onset was 100%.

CONCLUSION: There is a subjective component to scan interpretation that can have important implications for the clinical management of encephalitis cases. Neuroradiologists were good at diagnosing HSV encephalitis; however, agreement was worse for ADEM and other alternative aetiologies. Findings highlight the importance of a comprehensive and multidisciplinary approach to diagnosing the cause of encephalitis that takes into account individual clinical, microbiological, and radiological features of each patient.

Introduction

The prodrome of encephalitis is often non-specific, making it clinically difficult at an early stage to distinguish from other neurological syndromes. Both infectious and immune-mediated pathogeneses must be considered.[1] Approximately one-third of cases are immune-mediated, most frequently acute disseminated encephalomyelitis (ADEM), but also antibody-associated encephalitides, such as *N*-methyl-D-aspartate receptor antibody (NMDAR antibody) and voltage-gated potassium channel-complex antibody (VGKC-complex antibody) encephalitis.[2–4] Despite over 100 recognised causes, most studies fail to identify an aetiology in the majority of suspected cases.[5]

Management of acute encephalitis includes empirical initiation of antimicrobials. Following diagnostic investigations, these are rationalised and/or additional treatment instituted. Factors that complicate clinical decision making include falsely negative cerebrospinal fluid (CSF) polymerase chain reaction (PCR) results (particularly in herpes simplex virus [HSV] encephalitis) arising either from sampling too early or late or after institution of treatment; the availability of investigations; and lag time to results.[6]

Neuroimaging has a critical role in the evaluation of such patients. It aids diagnosis of encephalitis aetiology as well as mimicker conditions; it identifies complications (such as intracranial mass effect); and it may help prognostication. In patients with low probability of HSV encephalitis, Tyler[7] suggested that magnetic resonance imaging (MRI) findings later in the illness along with other clinical parameters could guide halting acyclovir. This is now incorporated in UK guidelines.[8]

Patterns of imaging abnormalities are described in cohorts of more common encephalitis aetiologies, such as HSV encephalitis.[9] In Japanese encephalitis, thalamic lesions on MRI are commonly seen, but the diagnosis is not excluded by their absence.[10] Most patients with autoimmune or paraneoplastic limbic encephalitis, for example, those associated with antibodies against the gamma-aminobutyric acid-B receptor (GABABR) or leucine-rich glioma inactivated protein 1 (LGI1), have an increased signal in the medial temporal lobes. The brain MRI is normal in approximately 60% of patients with anti-NMDAR encephalitis.[11] Very few studies have systematically investigated neuroimaging in all-cause encephalitis. Research is needed to better define associations between neuroimaging results and specific encephalitis aetiologies.

The aim of the present study was to assess the role of imaging in the early management of encephalitis and agreement on scan interpretation in a well-defined series of suspected encephalitis cases enrolled in the Prospective Aetiological Study of Encephalitis conducted by the Health Protection Agency (now incorporated into Public Health England [PHE]).

Materials and methods

Specific details regarding the study have been published elsewhere.[12] Patients with suspected encephalitis were recruited over a 2-year period (staged start between October 2005 and November 2006) from 24 hospitals in three geographical areas of England. Detailed clinical information was collected and each patient underwent extensive laboratory investigation. The case definition for encephalitis included any person of any age admitted to hospital with encephalopathy (altered level of consciousness persisting >24 hours, including lethargy, irritability, or a change in personality and behaviour) and two or more of the following: fever or history of fever (≥38°C) during the presenting illness; seizures and/or focal neurological findings (with evidence of brain parenchyma involvement); CSF pleocytosis (>4 white blood cells/μl); electroencephalogram (EEG) findings compatible with encephalitis; abnormal results of neuroimaging (computed tomography [CT]/MRI) in keeping with encephalitis.

Wherever possible, CT and MRI images were collected from each patient. This was only possible in a subset of recruiting centres due to practical complexities, including computer and software compatibility issues; however, all regions were represented. Available CT and MRI images were independently rated by three consultant neuroradiologists with expertise in reporting adult and paediatric neuroimaging. The raters were blinded to patient and clinical details and used a pre-defined proforma (see Electronic Supplementary Material), which included a checkboxed list of possible abnormalities.

Age, gender, and aetiology of patients with available CT and MRI images were compared to those in the entire PHE study cohort to assess sample representativeness. Differences in proportions were assessed by chi-squared or Fisher's exact test with a p-value of <0.05 considered statistically significant.