



Review

A systematic review of brain imaging findings in neurological infection with Japanese encephalitis virus compared with Dengue virus



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ABSTRACT

Objectives: Japanese encephalitis virus (JEV) and dengue virus (DENV) represent important causes of encephalitis in Asia. Brain imaging may provide diagnostic clues about the etiology of infectious encephalitis. We performed a systematic review of brain imaging findings in Japanese encephalitis (JE) and DENV neurological infection (dengue) to identify characteristic lesions.

Methodology: Five databases were searched. We included all study types and imaging techniques. Laboratory methods were categorized using diagnostic confidence levels. Imaging data were synthesized, and focal findings are presented as proportions for JE and dengue and for subgroups based on diagnostic confidence.

Principal findings: Thalamic lesions were the most reported magnetic resonance imaging finding in both diseases but appeared to occur more often in JE (74% in 23 studies) than dengue (29.4% in 58 studies). In cases diagnosed with antigen or nucleic acid tests, thalamic lesions were reported frequently in both JE (76.5% in 17 studies) and dengue (65.2% in 23 studies).

Significance: The results suggest that thalamic lesions frequently occur in both JE and dengue encephalitis. No radiological findings were found to be pathognomonic of either disease. Although brain imaging may support a diagnosis, laboratory confirmation with highly specific tests remains crucial.

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Introduction

Arthropod-borne viruses occur worldwide and pose major public health threats. This group of pathogens comprises a diverse range of virus genera and families (Arthropod-borne encephalitides - UpToDate, n.d.). Particularly damaging to human health are members of the genus *Flavivirus*, family *Flaviviridae*, which include Japanese encephalitis virus (JEV) and dengue virus (DENV) (Barrows et al., 2018). JEV and DENV are important causes of viral encephalitis in Asia (Hollidge et al., 2010; Turtle and

Solomon, 2018). Most JE cases occur in rural settings; however, urbanization and economic growth have led to an increasing geographical overlap with dengue (Nealon et al., 2019; Sakamoto et al., 2019). Dengue viruses were traditionally considered non-neurotropic, but cumulative evidence demonstrates that encephalitis does occur in a small proportion of patients such that it contributes to substantial morbidity and mortality (Carod-Artal et al., 2013). Diagnosing JEV and DENV neurological infection (from here on referred to as JE and dengue, respectively) is challenging for various reasons, namely cross-reactivity of antibody assays, non-specific clinical presentation, and establishing neuroinvasion. Brain imaging is becoming more widely available in Asia (Jankharia, 2008) and may contribute to diagnosis if specific lesions are identified for either disease.

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Japanese encephalitis

The worldwide number of people at risk of exposure to JEV is more than 4 billion (Campbell et al., 2011; Yun and Lee, 2014). There are an estimated 70,000 clinically symptomatic cases of JE every year with a case-fatality rate of approximately 30% and a further 30–50% of patients surviving with severe neurological disability (Campbell et al., 2011). The World Health Organization (WHO) recommends the collection of one or two cerebrospinal (CSF) samples to detect anti-JEV Immunoglobulin M (IgM) for diagnosis (WHO, 2018). Laboratory confirmation may also be performed by antigen detection, nucleic acid detection, or the ‘gold standard’ plaque reduction neutralization test (WHO, 2018).

Dengue

There are an estimated 50–100 million dengue cases annually, with up to 3.9 billion people living at risk of infection (Brady et al., 2012; Castro et al., 2017). Neurological impairment in dengue occurs either as a manifestation of severe organ impairment/shock (encephalopathy) or as a result of the viral invasion of the central nervous system (CNS) (encephalitis), which are difficult to differentiate clinically (Verma et al., 2014). Reverse transcription polymerase chain reaction (RT-PCR) in blood for the diagnosis of dengue is a highly sensitive and specific method, yet often unavailable in low- and middle-income countries. Dengue non-structural protein 1 (NS1) detection from blood is widely available as a rapid strip test and correlates well with the viral load (Muller et al., 2017). Inexpensive serological tests for dengue are available; more labor-intensive laboratory methods such as plaque reduction neutralization test can also be done in reference laboratories (WHO and Special Programme for research and Training in Tropical Diseases, 2009). Cross-reactivity of antibody-based diagnostic methods with other flaviviruses (e.g. JEV) is a common problem (Maeki et al., 2019).

Brain imaging in viral encephalitis

Viral encephalitides are clinically non-specific, and laboratory investigations may fail to detect the causative organism with acceptable sensitivity and specificity. Brain imaging adds additional diagnostic information (Maschke et al., 2004) and is recommended in the management of viral encephalitis (Britton et al., 2015; Sharma et al., 2012; Solomon et al., 2012). Thalamic lesions (often asymmetric) are the most frequently reported finding in JE (Kalita et al., 2016; Misra et al., 2008; Saini et al., 2014), and mid-brain lesions have been reported in 28–58% (Kalita et al., 2003; Misra et al., 2008). Evidence to support brain imaging features diagnostic of dengue neurological infection is poorly characterized (Carod-Artal et al., 2013; Saini et al., 2014; Verma et al., 2014). To the best of our knowledge, the present study is the first systematic review of the literature on brain imaging findings in JE and dengue aimed at identifying and quantifying characteristic lesions.

Materials and methods

This review was registered with PROSPERO (CRD42020171706) and conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Search strategy

Five databases (EMBASE®, MEDLINE®, Cochrane Library, Global Health, Web of Science™) were systematically searched using medical subject headings and terms relating to the keywords “Japanese encephalitis, dengue, and neuroimaging”. The strategy

was adjusted for each of the databases; the MEDLINE® search strategy is listed in Supporting Information Table S1. The literature search was performed on April 28, 2020, in which all databases and studies published until this date were assessed and included. Reference lists were downloaded into the reference manager Mendeley (London, United Kingdom). The reference lists of all included studies were scrutinized to identify any additional relevant material.

Inclusion and exclusion criteria

All study types were considered suitable. Studies with critical/high risk of bias were excluded. The following population, intervention, control, and outcomes criteria were applied for studies that reported brain imaging findings in infection with JE or dengue. Diagnostic tests were categorized into 3 confidence levels based on previous publications and WHO recommendations (Bharucha et al., 2020; Carod-Artal et al., 2013; WHO and Special Programme for research and Training in Tropical Diseases, 2009). Highly specific diagnostic methods such as polymerase chain reaction (PCR) were assigned confidence level 1. The least reliable diagnostic methods (e.g. single anti-DENV or anti-JEV antibodies in CSF) were grouped in confidence level 3 (see Table 4).

Population

Patients of any age with confirmed JEV infection (see Table 1) who underwent magnetic resonance imaging (MRI) or computed tomography (CT) head scan or other brain imaging.

Comparator

Patients of any age with confirmed acute dengue infection (see Table 2) who underwent MRI or CT head scan or other brain imaging.

Outcome

Pathologic features detected on brain imaging, differences between CT and MRI or other brain imaging, and distinguishing findings for either flavivirus infection.

Exclusion criteria

- Concurrent brain disease other than JE or dengue
- Authors report other CNS infections in the previous six months
- Abnormalities were reported on previous imaging, where applicable
- Brain imaging was performed 30 days or more after diagnosis
- Diagnosis based on single-serum anti-dengue or anti-JEV Immunoglobulin M (IgM) reading or single-serum sample seroneutralization or single high titer (hemagglutination-inhibition/complement-fixation/immunofluorescence).

Data extraction

The review software ‘DistillerSR’ by Evidence Partners Inc. (DistillerSR | Systematic Review and Literature Review Software by Evidence Partners, n.d.) was used for this systematic review. Titles and abstracts were screened, and studies that were clearly irrelevant were excluded. Subsequently, full texts were reviewed to select studies meeting the above-stated inclusion and exclusion criteria. Patients’ baseline characteristics, laboratory confirmation, brain imaging findings, and other criteria were extracted based on PRISMA (Moher et al., 2009) and STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) checklists (Von Elm et al., 2007).

Table 1
Japanese encephalitis virus infection diagnostic inclusion criteria

Confidence	Diagnostic test*	Specimen
Level 1	- JEV RNA (RT-PCR, RT-LAMP or WGS) - Virus isolation by inoculation	any any
Level 2	- JEV antigen detection (immunofluorescence or immunohistochemistry) - seroconversion or \geq fourfold rise in anti-JEV Ab (seroneutralization) – paired sera	CSF or brain tissue serum [†]
Level 3	- detection of neutralizing anti-JEV Ab - anti-JEV IgM - seroconversion or \geq fourfold rise in anti-JEV Ab (HI, CF, IFA) - seroconversion by ELISA – paired sera	CSF [†] CSF [†] serum [†] serum [†]

*Diagnostic tests performed on patients with suspected neurological infection

[†] Assays for dengue and/or other endemic flaviviruses should be done to rule out cross-reactivity. Ab = antibody; CF = complement fixation; ELISA = enzyme-linked immunosorbent assay; HI = hemagglutination inhibition; IFA = indirect immunofluorescence assay; RNA = ribonucleic acid; RT-LAMP = reverse transcription-loop-mediated isothermal amplification; RT-PCR = reverse transcription polymerase chain reaction; WGS = whole genome sequencing.

Table 2
Dengue virus neurological infection diagnostic inclusion criteria

Confidence	Diagnostic test*	Specimen
Level 1	- Dengue RNA (RT-PCR or WGS) - Dengue virus isolation by inoculation	any any
Level 2	- NS1 or other antigen detection (immunofluorescence or immunohistochemistry) - NS1 antigen detection - seroconversion or \geq fourfold rise in anti-dengue Ab (seroneutralization) – paired sera	CSF or brain tissue serum serum [†]
Level 3	- detection of neutralizing anti-dengue Ab - anti-dengue IgM - seroconversion or \geq fourfold rise in anti-dengue Ab (HI, CF, IFA) – paired sera - seroconversion by ELISA – paired sera	CSF [†] CSF [†] serum [†] serum [†]

* Diagnostic tests performed on patients with suspected neurological infection

[†] Assays for JEV and/or other endemic flaviviruses should be done out to rule out cross-reactivity. Ab = antibody; CF = complement fixation; ELISA = enzyme-linked immunosorbent assay; HI = hemagglutination inhibition; IFA = indirect immunofluorescence assay; NS1 = non-structural protein 1; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; WGS = whole genome sequencing.

Quality assessment

All studies included in this review were systematically assessed for risk of bias. Preliminary searches showed mostly observational studies. This was confirmed during the review process as all included studies were observational, with case reports the most frequently identified type of study. A recent review on the risk of bias assessment tools for primary and secondary medical studies recommended the Joanna Briggs Institute's (JBI) checklists for different types of observational studies (Ma et al., 2020). The risk of bias was therefore assessed using the JBI's checklists for cohort studies, analytical cross-sectional studies, case-control studies, case series, and case reports (ebp - Critical Appraisal Tools | Joanna Briggs Institute, n.d.). Studies categorized as having a high risk of bias were excluded (see below).

Qualitative and quantitative synthesis strategy

Comprehensive tables were used to list the characteristics and major findings from included studies and their risk of bias. After a recent publication on the synthesis of observational studies (Murad et al., 2018), quantitative data analysis was performed by calculating the proportions of reported imaging findings. Cohort, cross-sectional, and case-control studies were considered for meta-analysis. However, as populations, interventions, comparators, and outcomes differed considerably, this was deemed inappropriate. Recommendations from the 'synthesis without meta-analysis in systematic reviews reporting guideline' (Campbell et al., 2020) were followed for more transparent reporting.

Results

A total of 2591 records were identified after removing duplicates from the database search and additional records. Most full-text records assessed were in English; only one record was in

German and none in French, but 13 records were in other languages and thus excluded. A total of 99 studies were eligible according to the inclusion and exclusion criteria, but 7 records were removed for critical/ high risk of bias, leaving 92 included studies. The PRISMA flow diagram for all stages of the systematic review process is shown in Figure 1.

Risk of bias assessment

Figure 2 provides an overview of the risk of bias assessments using the JBI checklists for case reports, case series, analytical cross-sectional studies, cohort studies, and case-control studies (Moola et al., 2019). Supporting Information Tables S2 to S6 show the detailed risk of bias assessments for all included study types.

Study baseline and participants' characteristics

Overall, 24 studies described brain imaging findings in patients with JE and 68 studies reported on imaging in dengue infection. No study in which brain imaging findings were reported for both JE and dengue met the diagnostic inclusion criteria. Only observational studies were found that addressed the research question. Most included studies were case reports (dengue: 53/68 (77.9%), JE: 11/24 (45.8%)) and case series (dengue: 12/68 (17.6%), JE: 8/24 (33.3%)). Characteristics of all included studies according to study type are listed in Supporting Information Tables S7 and S8.

More studies reported on MRI findings than on CT findings (dengue: 58/68 (85.3%) vs 33/68 (48.5%), JE: 23/24 (95.8%) vs 14/24 (58.3%)). The most frequently described imaging technique in both flavivirus infections was T2-weighted fluid attenuation inversion recovery MRI (JE: 26%, dengue: 48%). No information was provided on the specific MRI technique used in 57% of JE and 34% of dengue publications.

The included studies provided data on a total of 211 and 125 patients who underwent any form of imaging for JE and dengue,

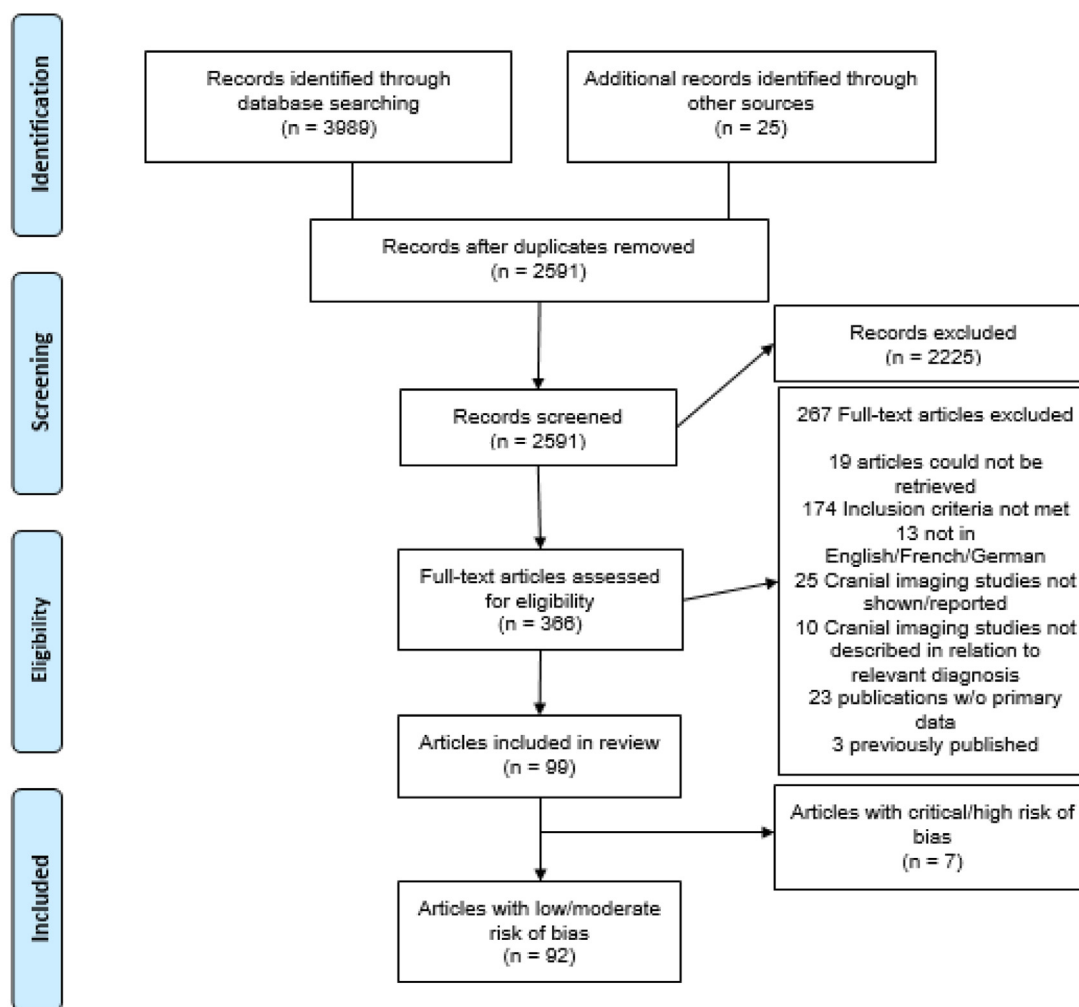


Figure 1. PRISMA flow diagram showing the stages of the systematic review process

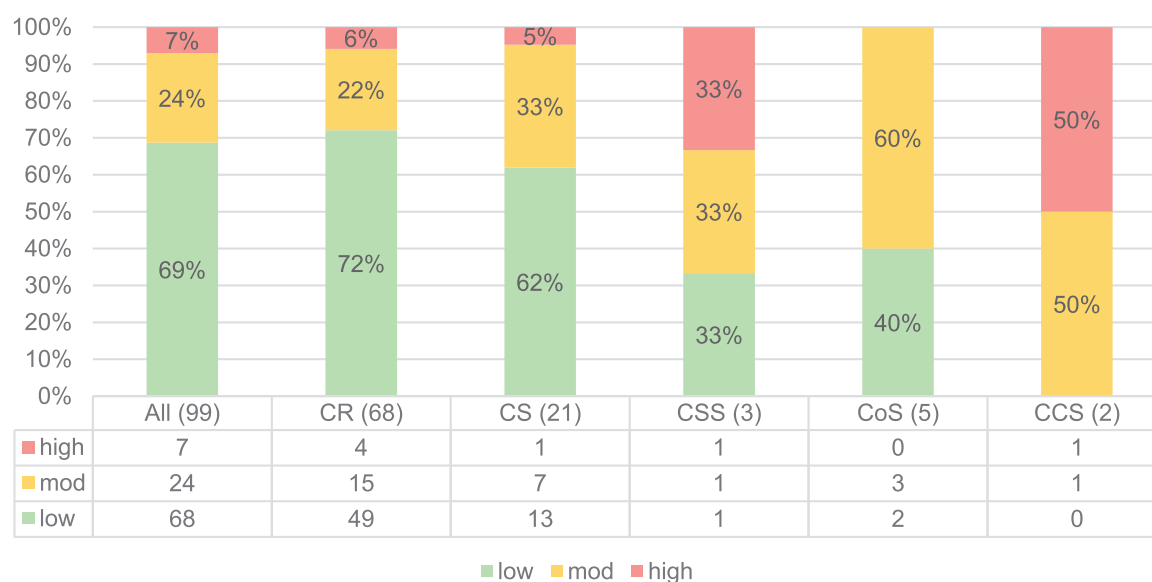


Figure 2. Risk of bias summary of all articles included in the review.

The numbers in brackets are the total numbers of assessed studies per study type. 'All' shows the combined risk of bias assessment result of all included studies. CCS = case-control study; CoS = cohort study; CR = case report; CS = case series; CSS = cross-sectional study.

Table 3
Overview of study baseline and participant characteristics

	Japanese encephalitis	Dengue infection
<i>Study characteristics</i>		
N included studies	24	68
Median publication year	2012	2016
Countries of origin*	IN: 9 (37.5%), JP 3 (12.5%), SG: 2 (8.3%)	IN: 38 (55.9%), MY: 6 (8.8%), SL: 6 (8.8%)
<i>Study type</i>		
Case report	11	53
Case series	8	12
Cohort study	4	1
Cross-sectional study	1	1
Case-control study	-	1
<i>Imaging techniques[†]</i>		
MRI only	10	35
CT only	1	10
MRI and CT	10	23
MRI and SPECT	3	-
<i>Participant characteristics</i>		
P	211	125
Age range	2 – 89 yr	5 m – 86 yr
Median age CR, CS [‡]	26 yr	25 yr
Gender ratio F:M CR, CS [‡]	1:1.6	1:1.7

*The three countries with the highest proportion of included studies are stated. [†] Imaging techniques that were used in included studies. [‡] Includes case reports and case series only. CCS = case-control study; CoS = cohort study; CR = case report; CS = case series; CSS = cross sectional study; CT = computed tomography; IN = India; JP = Japan; MRI = magnetic resonance imaging; MY = Malaysia; SG = Singapore; SL = Sri Lanka; SPECT = Single-photon emission computed tomography.

respectively. The patients' ages (case reports and case series only) were similar for JE and dengue (median age 26 years (2–89 years) vs 25 years (5 months–86 years)). The three most commonly reported neurological manifestations in both flavivirus infections were a reduced level of consciousness, headache, and seizure. A higher proportion of patients affected by dengue infection with neurological manifestations fully recovered (56.8%) compared with JE (33.6%). No clinical outcome was provided for almost a third of patients with JE (27.5%) compared with only 3.2% in dengue. An overview of the study baseline and participants' characteristics is listed in Table 3.

Summary of MRI and CT findings in JE and dengue neurological manifestation

A total of 181 (85.8%) patients with JE and 102 (81.6%) patients with dengue included in this systematic review underwent MR imaging. A total of 37 (17.5%) patients with JE and 42 (33.6%) patients with dengue had CT scans. In both flavivirus infections, a higher percentage of CT scans was reported as normal than MRI scans. However, this difference was more marked in JE (JE: 24.3% vs 4.4%, dengue: 35.7% vs 26.5%). Many focal lesions (i.e., cerebellar, basal ganglia, medial temporal lobe) were frequently identified on MRI scans but rarely on CT. Focal MRI lesions most often reported in JE were in the thalami (74%), basal ganglia (42.5%), and brain stem (32.6%). In dengue cases, the most commonly reported were thalamic lesions (29.4%), white matter lesions (28.4%), and brain stem lesions (19.6%). Intracranial hemorrhages were more common in dengue (MRI: 5.9%, CT 33.3%) than in JE (MRI 0.6%, CT 2.7%). Hemorrhages were the only imaging feature that was more frequently reported on CT scans than on MRI in both flavivirus infections Table 4. lists MRI and CT imaging findings for JE and dengue cases.

MRI findings in JE and dengue encephalitis

We compared MR imaging characteristics between JE and dengue encephalitis cases in which an acute infection of the CNS was proven by CSF analysis (CSF anti-IgM, CSF seroneutralization, or CSF PCR). Cases were allocated according to the diagnostic level of confidence (level 1 and 2 'L1/2' vs level 3 'L3', see Tables 1 and 2 of the Methods section). There were more JE cases (n=95) than dengue cases (n=59), in which diagnostic evidence for a CNS infection was provided (Table 5). Thalamic lesions, which have been suggested to be a characteristic feature of JE (Misra and Kalita, 2010a), were common in both groups of diagnostic confidence (76.5% vs 79.5%) of JE. A marked difference was found for dengue cases, in which 14/22 (63.6%) of the higher diagnostic confidence group showed thalamic lesions, compared with only 3/36 (8.3%) in the lower group. Of note, the proportion of cases in which thalamic lesions were seen on MRI appears comparably high for both JE and dengue for cases with positive nucleic acid and/or antigen test (L1/2: 76.5% vs 63.6%). A similar pattern was found for brainstem lesions. Many focal lesions (i.e., cerebral white matter, cerebellum, minor intracranial hemorrhage) were reported more frequently in the dengue encephalitis L1/2 group than in the lower diagnostic confidence L3 group.

The spectrum of MRI findings associated with dengue infection

Table 6 lists an overview of specific features in dengue encephalitis, dengue encephalopathy, acute disseminated encephalomyelitis, and other dengue-related neurological manifestations according to the diagnosis provided by the study authors. Overall, there were more abnormal findings on MRI imaging in the encephalitis group than in any other group. Thalamic lesions were described in 25 cases (56.8%) classified as dengue encephalitis. A total of 75% (6/8) of acute disseminated encephalomyelitis cases showed cerebral white matter lesions. Only one case in the group of other dengue-associated neurological manifestations had abnormal imaging findings.

Discussion

This systematic review identified 92 studies reporting imaging findings in neurological infection with JEV or DENV. JE appears to be the better-studied disease in this field with a higher quality of observational studies available, whereas, to date, brain imaging studies on dengue are restricted to case reports and case series. Diagnostic confirmation was variable, and the studies were grouped into three categories of diagnostic confidence. Overall, the results suggest that there are focal lesions associated with both flavivirus infections. However, there is a lack of evidence that brain imaging can differentiate between the two diseases. Furthermore, the subgroup analysis according to diagnostic confidence suggested there is a difference in patients in whom a diagnosis of DENV encephalitis is made by the detection of DENV specific IgM alone in CSF and highlights the need for improved diagnostic standards. Possibly these patients do not have as severe neurological disease, for example, they have encephalopathy, not encephalitis, or they have been imaged at a different point in the natural history of the illness.

The most frequently used imaging technique was MRI (JE: 23/24, dengue: 58/68), followed by CT (JE: 11/24, dengue 33/68). In this review, more focal lesions were identified on MRI than on CT in both diseases. This is in keeping with previous publications on infectious encephalitis as MRI scans provide better soft tissue contrast than CT scans (Gupta et al., 2012; Md Noh et al., 2018). The number of normal MRI scans was markedly higher in dengue

Table 4
MRI and CT imaging findings according to diagnosed flavivirus infection

	JE (P=211)	CT	Dengue * (P=125)	CT
	MRI		MRI	
Total N [†] (% P)	181 (85.8%)	37 (17.5%)	102 (81.6%)	42 (33.6%)
Normal scan n (%N)	8 (4.4%)	9 (24.3%)	27 (26.5%)	15 (35.7%)
Focal lesions				
Thalamus	134 (74.0%)	11 (29.7%)	30 (29.4%)	6 (14.3%)
Cerebral cortex	21 (11.6%)	4 (10.8%)	9 (8.8%)	-
Cerebral white matter	11 (6.1%)	-	29 (28.4%)	2 (4.8%)
Basal ganglia	77 (42.5%)	1 (2.7%)	8 (7.8%)	1 (2.4%)
Substantia nigra	13 (7.2%)	-	-	-
Caudate nucleus	22 (12.2%)	-	2 (1.9%)	-
Putamen	22 (12.2%)	-	-	-
Globus pallidus	14 (7.7%)	-	4 (3.9%)	-
Ns	41 (22.7%)	1 (2.7%)	2 (1.9%)	1 (2.4%)
Brainstem	59 (32.6%)	1 (2.7%)	20 (19.6%)	3 (7.1%)
Midbrain	48 (26.5%)	-	6 (5.9%)	-
Pons	10 (5.5%)	-	12 (11.8%)	3 (7.1%)
Ns	2 (1.1%)	-	6 (5.9%)	-
Medial temporal lobe	32 (17.7%)	1 (2.7%)	5 (4.9%)	-
Hippocampus	29 (16.0%)	-	2 (1.9%)	-
Ns	3 (1.7%)	-	3 (2.9%)	-
Cerebellum	5 (2.8%)	-	19 (18.6%)	-
Meningeal enhancement	23 (12.7%)	1 (2.7%)	2 (1.9%)	-
Generalized cerebral edema	1 (0.6%)	4 (10.8%)	14 (13.7%)	4 (9.5%)
Generalized atrophy	-	10 (27.0%)	-	-
ADEM	-	-	6 (5.9%)	-
Intracranial hemorrhage				
major	1 (0.6%)	1 (2.7%)	6 (5.9%)	14 (33.3%)
minor	-	-	12 (11.7%)	-
Ischemic stroke	1 (0.6%)	1 (2.7%)	3 (2.9%)	-

*Includes all dengue cases with various neurological manifestations. [†] N total number of patients who underwent respective neuroimaging. P = Total number of included participants. ADEM = acute disseminated encephalomyelitis; CT = computed tomography; MRI = magnetic resonance imaging; ns = not specified.

Table 5
MRI findings of JE and dengue encephalitis cases in which a CNS infection was detected in CSF or brain tissue, according to diagnostic confidence level

	Japanese encephalitis*		Dengue encephalitis*	
	L1/2	L3	L1/2	L3
Total N [†]	17	78	22	36
Focal lesions (%N)				
Thalamus	13 (76.5%)	62 (79.5%)	14 (63.6%)	3 (8.3%)
Cerebral cortex	4 (23.5%)	16 (20.5%)	3 (13.6%)	1 (2.8%)
Cerebral white matter	-	4 (5.1%)	9 (40.1%)	2 (5.6%)
Basal ganglia	6 (35.3%)	37 (47.4%)	2 (9.1%)	1 (2.8%)
Brainstem	4 (23.5%)	32 (41.0%)	8 (36.4%)	1 (2.8%)
Medial temporal lobe	11 (64.7%)	2 (2.6%)	3 (13.6%)	-
Hippocampus	8 (47.1%)	1 (1.3%)	-	-
Ns	3 (17.6%)	-	3 (13.6%)	-
Cerebellum	-	2 (2.6%)	9 (40.1%)	3 (8.3%)
Meningeal enhancement (%N)	2 (11.8%)	-	1 (4.5%)	-
Gen. cerebral edema (%N)	-	1 (1.3%)	1 (4.5%)	12 (33.3%)
Generalized atrophy (%N)	-	-	-	-
ADEM (%N)	-	-	2 (8.7%)	-
Intracranial hemorrhage (%N)	-	-	8 (36.4%)	2 (5.6%)
major	-	-	-	-
minor	-	-	8 (36.4%)	2 (5.6%)
Ischemic stroke (%N)	-	-	-	-

*Studies in which a diagnosis was based on serum investigations alone were excluded. See Tables 1 and 2 for details on levels of diagnostic confidence. [†] N total number of patients with respective flavivirus infection and diagnostic confidence level who underwent magnetic resonance imaging. ADEM = acute disseminated encephalomyelitis; CT = computed tomography; MRI = magnetic resonance imaging; ns = not specified.

with neurological manifestations than in JE, suggesting that a significant proportion of included patients with dengue suffered encephalopathy rather than encephalitis. T2-weighted fluid attenuation inversion recovery (T2-FLAIR) was the most often reported MRI sequence across all studies on JE and dengue. Misra *et al.* directly compared and evaluated various MRI sequences in patients

with viral encephalitis, among them JE, dengue, and herpes simplex encephalitis cases and concluded that T2 and T2-FLAIR were the most useful sequences (Misra *et al.*, 2010). This finding is supported by the results of this review, and future studies on flavivirus encephalitis should consider T2-FLAIR sequences when investigating characteristic focal lesions on MRI. The advantages of using CT

Table 6

MRI findings in dengue encephalitis compared with dengue encephalopathy, ADEM and other dengue-associated CNS pathologies according to study authors*

	Dengue encephalitis*	Dengue encephalopathy*	ADEM	Other†
Total N†	44	13	8	11
Focal lesions (%N)				-
Thalamus	25 (56.8%)	1 (7.7%)	3 (37.5%)	-
Cerebral cortex	7 (15.9%)	1 (7.7%)	2 (25.0%)	-
Cerebral white matter	19 (43.2%)	4 (6.7%)	6 (75.0%)	1 (9.1%)
Basal ganglia	5 (11.4%)	-	2 (25.0%)	1 (9.1%)
Brainstem	14 (31.8%)	4 (30.8%)	2 (25.0%)	-
Medial temporal lobe	6 (13.6%)	-	-	-
Hippocampus	2 (4.5%)	-	-	-
ns	4 (9.1%)	-	-	-
Cerebellum	16 (36.4%)	2 (15.4%)	-	-
Meningeal enhancement (%N)	5 (11.4%)	-	-	-
Gen. cerebral edema (%N)	1 (2.3%)	-	-	-
Intracranial hemorrhage (%N)				
major	2 (4.5%)	2 (15.4%)	1 (12.5%)	1 (9.1%)
minor	11 (25.0%)	2 (15.4%)	1 (12.5%)	-
Ischemic stroke (%N)	-	1 (7.7%)	-	-

Participants were grouped according to the author's diagnosis. Eight studies (26 patients) did not provide a diagnosis and were excluded from this subgroup analysis. † N total number of patients who underwent MRI in the respective group of Dengue infection. ‡ Other Dengue-associated pathologies. Includes cases of neuritis, cranial nerve palsies, and early Guillain-Barre syndrome. ADEM = acute disseminated encephalomyelitis; CT = computed tomography; MRI = magnetic resonance imaging; ns = not specified.

over MRI scans are the faster acquisition time, wider availability in low- and middle-income countries, and the ability to pick up important differential diagnoses such as hemorrhages or abscesses (Chowdhury et al., 2010; WHO, 2014). It can thus be expected that CT brain scans will continue to play a role in the diagnosis of acutely unwell patients with suspected viral encephalitis despite its inferiority in detecting focal soft tissue lesions.

The results of this systematic review suggest that thalamic lesions may be the most common focal finding on MRI scans in both JE and dengue neurological infections. Previous reports of the proportion of thalamic lesions on MRI in JE vary between 56% and 94% (Lo et al., 2019; Misra and Kalita, 2010b). In a 2011 review, Handique et al. found that the most commonly affected brain regions on MRI in JE were the thalami, substantia nigra, and basal ganglia (Handique, 2011). However, thalamic lesions may not be considered pathognomonic of these diseases, as they have been described in other CNS infections, for example, West Nile virus (Ali et al., 2005), Herpes simplex virus type 1 and Epstein-Barr virus (Beattie et al., 2013). Comparing the synthesized MRI findings of JE to dengue encephalitis for cases with high diagnostic confidence, there may be other focal lesions better suited to provide diagnostic clues. White matter lesions, cerebellar lesions, and minor intracranial hemorrhages were reported frequently in dengue encephalitis but never in JE. Basal ganglia and hippocampus lesions were reported much more frequently in JE than in dengue encephalitis.

The spectrum of dengue brain imaging findings is particularly interesting as dengue neurological manifestations may be caused by a variety of underlying virus-related pathologies (Channa and Wasay, 2006). Dengue brain imaging features remain poorly characterized to date (Bhoi et al., 2014; Li et al., 2017; Saini et al., 2014). In the present study, imaging findings across all cases of dengue-associated neurological manifestation showed thalamic lesions in less than 30%. Interestingly, thalamic lesions occurred in almost two-thirds (65.2%) of cases in which a laboratory confirmation of dengue CNS infection with high diagnostic confidence was provided. When comparing what are regarded as solid diagnoses for JE and dengue, accepting the differences in making these diagnoses, there appear to be more thalamic lesions found on imaging in JE than in dengue, whereas the group diagnosed by CSF dengue antibody alone appeared distinctly different. This sug-

gests a fundamental difference between JEV and DENV in terms of the performance of CSF IgM assays or that DENV neurological disease forms distinct entities with different pathogenic mechanisms. There are currently two diagnostic standards for dengue encephalitis. Carod-Artal et al. proposed neurological symptoms, presence of DENV RNA, antigen or antibodies in CSF, and CSF pleocytosis without other causes of infectious encephalitis for diagnosing dengue encephalitis (Carod-Artal et al., 2013). In 2014, Soares et al. raised concerns that the previously mentioned diagnostic criteria may be specific but suffered poor sensitivity (Soares and Puccioni-Sohler, 2014). They proposed different dengue encephalitis diagnostic criteria, including the presence of fever, acute signs of CNS involvement, reactive IgM dengue antibody, NS1 antigen, or positive dengue PCR in serum and/or cerebrospinal fluid, whereas excluding other causes of viral encephalitis (Soares and Puccioni-Sohler, 2011). Soares et al. intended to provide a more sensitive diagnostic tool for dengue encephalitis. Yet, the results of the present systematic review suggest that the specificity of the diagnostic method is crucial in identifying characteristic lesions on brain imaging in dengue infection. The wide acceptance of the diagnostic criteria by Soares et al. may be overinclusive (Kumar et al., 2017; Kutiya, 2017; Ng and Sadarangani, 2017). Both currently used diagnostic standards for dengue encephalitis are insufficient. It is possible that IgM detected in CSF may be because of a bloody tap, non-specific reactivity, or a leaky blood-brain barrier (Puccioni-Sohler et al., 2009; Chen et al., 1991). This may be evaluated by measuring the albumin quotient and antibody index; however, this requires sufficient laboratory capacity. Moreover, the timepoint of diagnosis and sampling in the course of the disease may be crucial.

The present study is the first systematic review that synthesizes all brain imaging data published to date in English, German, and French on neurological infection with JEV and DENV. To the best of our knowledge, no systematic review on a comparable scale of brain imaging in these two flavivirus infections has been published previously. In addition, we present proportions of focal lesions found on brain imaging studies in dengue neurological infection for the first time and evaluate the level of diagnostic confidence in cases of JE and dengue neurological infection. By correlating brain imaging findings with these confidence levels, the present study provides evidence that reliable, specific laboratory investigations are key for an accurate diagnosis of the respective

flavivirus infection. In particular, it appears that CSF IgM measurement is more reliable for the diagnosis of JE than for dengue encephalitis. The high specificity of brain imaging data was achieved by applying strict diagnostic criteria in all confidence levels and excluding studies that provided single antibody-positive serum samples solely. According to Bharucha *et al.*, only 13% of all publications on JE cases use diagnostic methods of confidence level 1 or 2 (Bharucha *et al.*, 2020).

There are several limitations to this systematic review. First, a high selection bias must be assumed as 64 case reports formed a major part of the body of evidence in which imaging findings were synthesized. The availability of brain imaging is most likely unevenly distributed in low- and middle-income countries, and many patients with JE or dengue neurological manifestation will never receive a scan. Depending on the setting, this may be exacerbated by financial barriers. Reviewed together, the sample of the present study cannot be considered representative of any population, which limits the generalizability. Furthermore, studies may have published results for specific MRI sequences, which led to reporting bias. Depending on the objectives of a study, focal lesions may have been reported for specific parts of the brain, omitting other abnormal findings deemed less important. Concurrent brain infection other than JE or dengue, which was stated as an exclusion criterion but may not have been detected, may be a confounder. The diagnostic confidence levels used in this systematic review were originally developed by Bharucha *et al.* for JE and adapted for dengue neurological infection (Bharucha *et al.*, 2020). The comparability between the different levels of diagnostic confidence in the two diseases may be limited, as the availability of rapid antigen tests makes it easier to diagnose dengue compared with JE. A further limiting factor is the risk of bias assessment of the different study types. All observational study types were considered equal regarding the baseline quality of evidence, and their exclusion or inclusion was based on the risk of bias rating. This decision was made because the risk of bias of the cross-sectional and case-control studies that comprised the included cohort was mostly moderate to high, whereas many case reports and case series provided a lower risk of bias and higher quality brain imaging reports. A total of 12 studies were excluded from this systematic review because they were not in English, French, or German. Abstracts available in English for some of these studies show that a number of relevant observational studies are available in Korean, Mandarin, and Japanese. Given the scarcity of data on neuroimaging in flavivirus infection, a systematic review including all publications in East Asian languages would be worthwhile. Brain imaging studies comparing JE and dengue neurological infection will remain challenging as most JE cases occur in rural settings away from centers with MRI and CT facilities. However, a prospective study comparing these two flavivirus infections that combines a detailed diagnostic workup using high-confidence methods with a clear timeline on clinical presentation, sampling, and brain imaging is needed. This would contribute to establishing brain imaging as a valuable added diagnostic feature in JEV and DENV neurological infection, benefiting patients and clinicians in their daily practice.

Conflict of Interests declaration

We have no conflicts of interest to disclose.

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Ethical Approval Statement

Ethical approval was not required for this systematic review.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2022.03.010](https://doi.org/10.1016/j.ijid.2022.03.010).

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