International Journal of Biomedical Research
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: https://doi.org/10.7439/ijbr
CODEN: IJBRFA

Original Research Article

Neuroimaging evaluation of pattern of brain involvement in Japanese encephalitis and other viral encephalitis in paediatric age group

Shyam Lal Agarwal[1], Mrinalkanti Ghosh[*1], Shadab Afroze[1], Anirbaan Palit[1], Aniruddha Ghosh[1] and Kaustav Nayek[2]

[1]*Department of Radiodiagnosis, Burdwan Medical College, Burdwan, India*
[2]*Department of Paediatrics, Burdwan Medical College, Burdwan, India*

QR Code

***Correspondence Info:**
Dr. Mrinalkanti Ghosh
Associate Professor,
Department of Radiodiagnosis,
Burdwan Medical College, Burdwan, WB, India

***Article History:**
Received: 14/03/2018
Revised: 04/04/2018
Accepted: 04/04/2018
DOI: https://doi.org/10.7439/ijbr.v9i4.4694

Abstract

Introduction: Japanese encephalitis virus, a flavivirus is a significant cause of arboviral encephalitis worldwide. The virus is transmitted to humans via the bite of infected *Culex* mosquitoes especially *C. tritaeniorhynchus*, they prefer to bite outdoors and are extremely active and are extremely active in the evening and night. Neuroimaging reveals by MRI and CT scan of patients of Japanese encephalitis shows characteristic lesions particularly in the thalami, substantia nigra, basal ganglia, cerebral cortex, cerebellum, brainstem and white matter.

Material & Method: A total of 50 patients divided in 25 anti JE antibody positive patients and another 25 in anti JE antibody negative group. A cross sectional observational analytical study was performed in the time period of January 2015 to August 2016, the patients was studied using IgM capture ELISA and 1.5T MRI machine.

Result Analysis: The results were analysed using chi square test and p values. It was found that gray matter structures were the most commonly affected, the thalamus, basal ganglia but white matter lesions were also noted. The thalamus was the most commonly involved structure, followed by the brainstem and cerebral cortex. Haemorrhagic lesions were noted in the cortex, midbrain and cerebellum.

Conclusion: Involvement of the thalamus showed the most significant difference between JE and non JE patients with 64% of the JE patients showed thalamic involvement. No other part of the brain showed such significant difference.

Keywords: Neuroimaging, Paediatric, Japanese Encephalitis.

1. Introduction

Japanese encephalitis virus, a flavivirus (single-stranded ribonucleic acid [RNA]), represents the most significant etiology of arboviral encephalitis worldwide. Japanese encephalitis virus belongs to the Japanese encephalitis serocomplex, which is composed of 9 genetically and antigenically related viruses of the *Flaviviridae* family. JE serocomplex flaviviruses include Alfuy virus, Cacipacore virus, Japanese encephalitis virus, Koutango virus, Murray Valley encephalitis virus, Saint Louis encephalitis virus, Usutu virus, West Nile virus including Kunjin virus, and Yaounde virus [1].

In 1934, a Japanese scientist, Hayashi, inoculated monkey brains with the virus, reproducing the disease. This virus was named Japanese B encephalitis virus, after its association with the summer type (or type B) encephalitis.

Japanese encephalitis virus is transmitted to humans via the bite of infected *Culex* mosquitoes, especially *C tritaeniorhynchus*. Other *Culex* vectors include *Culex vishnui* (India), *Culex gelidus*, and *Culex fuscocephala* (Thailand, India, Malaysia). They prefer to bite outdoors and are extremely active in the evening and night, when the risk of infection is greatest.

Mosquitoes breed in collections of water (typically rice paddies), increasing the risk of infection in rural areas. *Aedes* mosquitoes have also been implicated in Japanese encephalitis virus infection.

Humans are incidental and dead-end hosts, producing a low-grade, short-term viremia. Therefore, mosquitoes are unable to transmit the virus from one person to another.

Pigs and aquatic birds (e.g., egrets, herons) serve as amplifying hosts. They develop persistent, high-grade viremia and represent the main vertebrate hosts and the principal reservoir for the virus. Cattle develop only relatively low-grade viremia or none at all; these animals are not part of the natural transmission cycle of the virus.

The main genotypic variants of Japanese encephalitis virus include the following [2] Japanese encephalitis virus genotype I isolates have been identified in northern Thailand, Cambodia, and Korea.

- Japanese encephalitis virus genotype II isolates have been identified in southern Thailand, Malaysia, Indonesia and Northern Australia.
- Japanese encephalitis virus genotype III isolates have been identified in Japan, China, Taiwan, Philippines, and the Asian subcontinent, including India and Nepal.
- Japanese encephalitis virus genotype IV isolates have been identified in Indonesia.
- Japanese encephalitis virus genotype V isolate have been identified in 1952 from a patient who originated in Muar, Malaysia (Muar strain). There is a report of its possible reemergence in the Republic of Korea.

A myriad of factors govern the severity of JEV pathogenesis. The failure of the host to produce antibodies against the virus is associated with an increased likelihood of the disease to turn lethal [3]. Crossing the blood–brain barrier is an important factor in the increased pathogenesis and clinical outcome of the neurotropic viral infection [4]. After entering the body through a mosquito bite, the virus reaches the central nervous system (CNS) via leukocytes (probably T lymphocytes), where JEV virions then bind to the endothelial surface of the CNS and are internalized by endocytosis[5] however, it is still not clear whether macrophages and B lymphocytes can also harbor JEV. In other flaviviral infections, such as WNV, macrophages could serve as a reservoir, spreading the virus from the peripheral areas to the CNS[6]. Studies have shown that WNV is capable of entering the CNS through anterograde axonal transport[7]. Because both WNV and JEV belong to the same family of viruses [8-10], macrophage and axonal transport may play a critical role in JEV pathogenesis; however, convincing evidence is still lacking.

On MR imaging and CT, Japanese encephalitis shows lesions in the thalami, substantianigra, basal ganglia, cerebral cortex, cerebellum, brain stem, and white matter whereas temporal lobe involvement is characteristically seen in Herpes simplex encephalitis (HSE). Temporal lobe involvement in JE may cause problems in differentiating it form HSE [11]. MR imaging differentiates both HSE and JE by locating the typical sites of involvement of each virus. The deep gray matter involvement is an important distinguishing feature of Japanese encephalitis from herpetic encepahilitis in which cortical involvement occurs predominantly. MR imaging is extremely sensitive in detecting both thalamic and extrathalamic lesions. Moreover, it identifies the petechial haemorrhage associated with HSE and the overt haemorrhage seen in most lesions of JE. DW images demonstrate the cytotoxic edema and restricted diffusion [12].

1.1 Objective

To determine the areas of brain involvement in JE virus encephalitis and non JE virus encephalitis.

2. Materials and methodology

Patients below the age of 15 years, having features of encephalitis presenting to the department of paediatrics, Burdwan Medical College and Hospital. Total 50 cases (25 cases of anti JE antibody positive patients and 25cases of anti JE antibody negative patients). The study period was January 2015 to August 2016. An analytical study, patients with clinical features of viral encephalitis were provided with questionnaire and examined with predesigned and pretested schedule and were selected for study population with certain exclusion and inclusion criteria.

Tools for the study included IgM capture ELISA kit for Japanese Encephalitis and 1.5T MRI machine.

2.1 Inclusion criteria

- Children ≤15 years
- Presenting with altered sensorium

2.2 Exclusion criteria

- Patients of simple febrile convulsion
- Patients of pyogenic meningitis
- Patients of tubercular meningitis
- Patients in shock following diarrhea or vomiting
- Patients of head injury
- Patients of metabolic encephalopathy

2.3 Methodology

Patients admitted with features of encephalitis are subjected to their serum and CSF test for detection of IgM antibody against je virus. Subsequently their brain MRI was performed. The GCS of the patient is calculated. Consent is obtained from the party before including the patient in the study. Selected patients are allocated into two groups- one in which test for anti JE antibody is positive and other in which the test for anti JE antibody is negative. The findings of the brain CT SCAN and MRI of the above two groups are compared. The imaging findings are then compared to observe the areas of brain involved.

2.4 Statistical methods

All data of the study will be analyzed by applying different statistical techniques like chi-square test, p value etc.

3. Results

Table 1: Thalamic Involvement: In the present study the ratio of thalamic involvement

Thalamus	JE Positive (n=25)	JE Negative (n=25)	P Value
Involved	16	4	0.0015
Not Involved	9	21	

No thalamic involvement in JE positive and JE negative patients are 16:9 and 4:21 respectively. There is significant difference between the two group (p=.0015)

Figure 1: Showing ratio of thalamic involvement in JE positive and JE negative patients

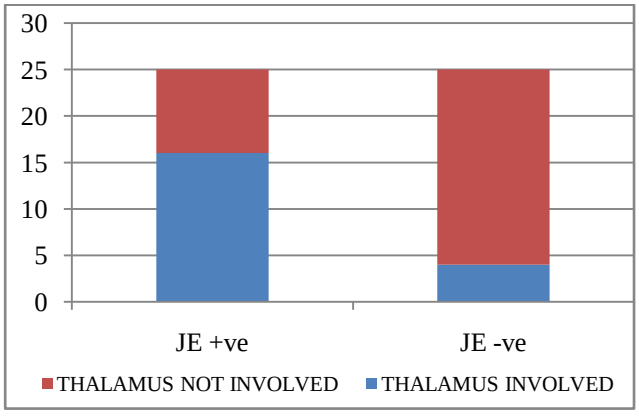

Table 2: Cerebellar Involvement: In the present study the ratio of cerebellar involvement in JE positive and JE negative patients are

Cerebellum	JE Positive (n=25)	JE Negative (n=25)	P Value
Involved	3	9	0.097
Not involved	22	16	

Figure 2: Showing ratio of cerebellar involvement in JE positive and JE negative patients

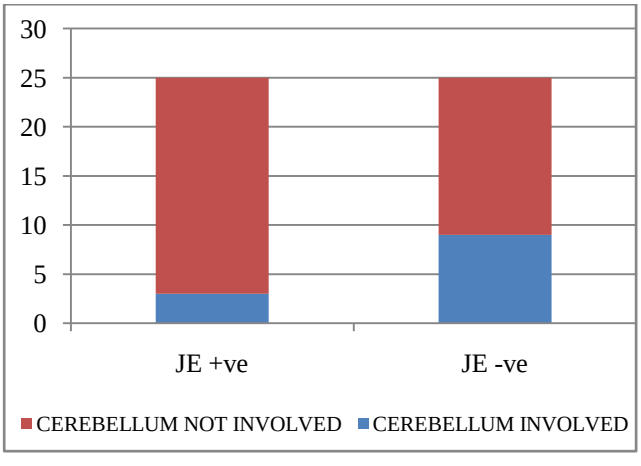

Table 3: Basal Ganglia Involvement: In the present study the ratio of basal ganglia involvement in JE positive and JE negative patients are

Basal ganglia	JE positive (n=25)	JE negative (n=25)	P value
Involved	3	2	P=1.00
Not involved	22	23	

Figure 3: Showing ratio of basal ganglia involvement in JE positive and JE negative patients

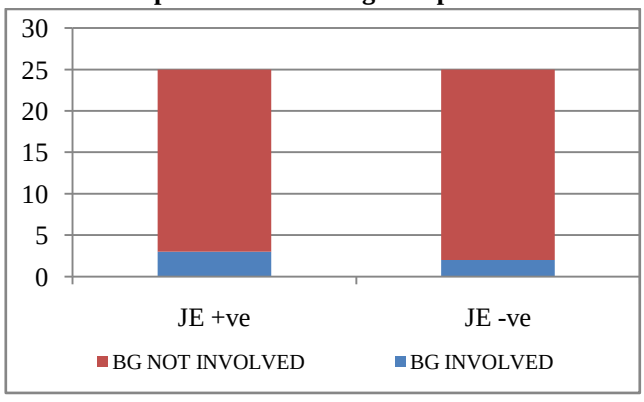

Table 4: No brain involvement: In the present study the ratio of normal brain MRI in JE positive and JE negative patients are

MRI brain	JE Positive (n=25)	JE Negative (n=25)	P Value
Normal	8	6	0.75
Abnormal	17	19	

Figure 4: Showing ratio of normal MRI brain in JE positive and JE negative patients

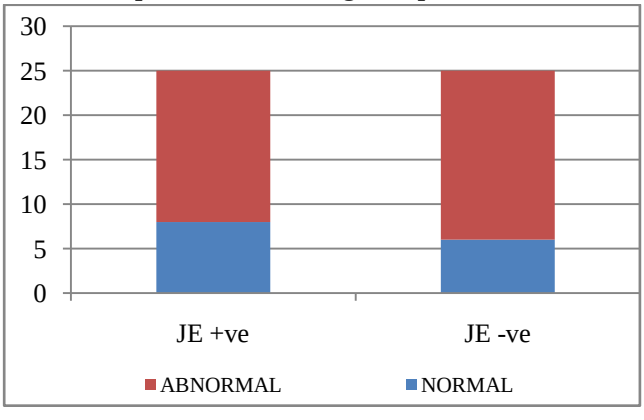

Table 5: Chart showing percentage of parts of brain involved

Part of brain	JE Positive	JE Negative
Thalamus	64%	16%
Cerebellum	12%	36%
CC	24%	4%
BS	48%	64%
BG	12%	8%
WM	20%	16%
Normal	32%	24%

4. Discussion

In our study in 9 of 10 patients, either diffuse or patchy white matter lesions were observed bilaterally, together with abnormalities in areas such as the thalamus, basal ganglia, and brainstem. This study indicates that Japanese encephalitis can produce white matter involvement, although gray matter structures such as the thalamus, basal ganglia, and brainstem are more severely

affected. In our study 16 out of 25 je patient showed thalamic involvement and only 4 out of 25 non je patient showed thalamic involvement (p=0.0012) which is significant[13].

In another study done by Kumar *et al* in 1997 MRI was carried out on a 1.5 T system within 10-60 days of onset. In all the patients MRI revealed bilateral thalamic lesions, haemorrhagic in five. Signal changes were present in the cerebrum in four patients, the midbrain and cerebellum in three each, the pons in two and the basal ganglia in one. The lesions were haemorrhagic in three of the four patients with lesions in the cortex, two of the three with lesions in the midbrain and cerebellum, but the pontine lesions were haemorrhagic in both patients. Spinal cord involvement was seen in one of the three patients who underwent MRI. However no hemorrhagic transformation was seen in our study [14].

In a study done in March 2000 by Misra *et al*, 31 Japanese encephalitis patients underwent MRI which was found to be abnormal in all 31 patients including 17 with normal CT scan. Cranial MRI revealed either mixed intensity or hypointense lesion on T (1) and hyperintense or mixed intensity lesion on T2 in thalami in all except two patients. The MRI lesions were also noted in basal ganglia in 11, midbrain in 18, pons in 8, cerebellum and cerebral cortex in 6 patients each and subcortical white matter in 2 patients which showed strong association between JE encephalitis and thalamic and brainstem involvement similar to our study[15]. The strength of our study was the well-equipped Department of Radiology and Paediatrics at our institution which caters a huge number of patients from all over West Bengal. So we get a large no. of referral cases. But due to constrain of the time period of the study we could only accumulate 50 cases which were successfully followed up. Among all such inconveniences, we could complete our study anyways & we hope to carry the study further with accumulation of significant no. of cases in some future date.

5. Conclusion

A cross sectional observational type of analytical study was carried out in the Department of Radiodiagnosis in Burdwan Medical College & Hospital from January 2015 to August 2016, over 50 cases, in patients below the age of 15 years presenting with features of encephalitis in the Department of Paediatrics, Burdwan Medical College & Hospital. All Patients admitted with features of encephalitis were subjected to their serum and CSF test for detection of IgM antibody against je virus. Subsequently their brain MRI was performed. The GCS of the patients were calculated.

Selected patients were allocated into two groups- one in which test for anti JE antibody is positive and other in which the test for anti JE antibody is negative. The findings of the brain CT SCAN and MRI of the above two groups were compared.

The parts of brain involved in Japanese encephalitis patients were in the following order thalamus > brainstem > normal > cerebral cortex > white matter > basal ganglia = cerebellum. Brainstem > cerebellum > normal > thalamus = white matter > basal ganglia > cerebral cortex.

There was a significant difference in the percentage of patients showing thalamic involvement in the two groups with thalamus being involved in 64% of Japanese encephalitis patients and in 16% of non JE viral encephalitis patients.(p=0.0015). No other part of the brain showed a significant difference in involvement.

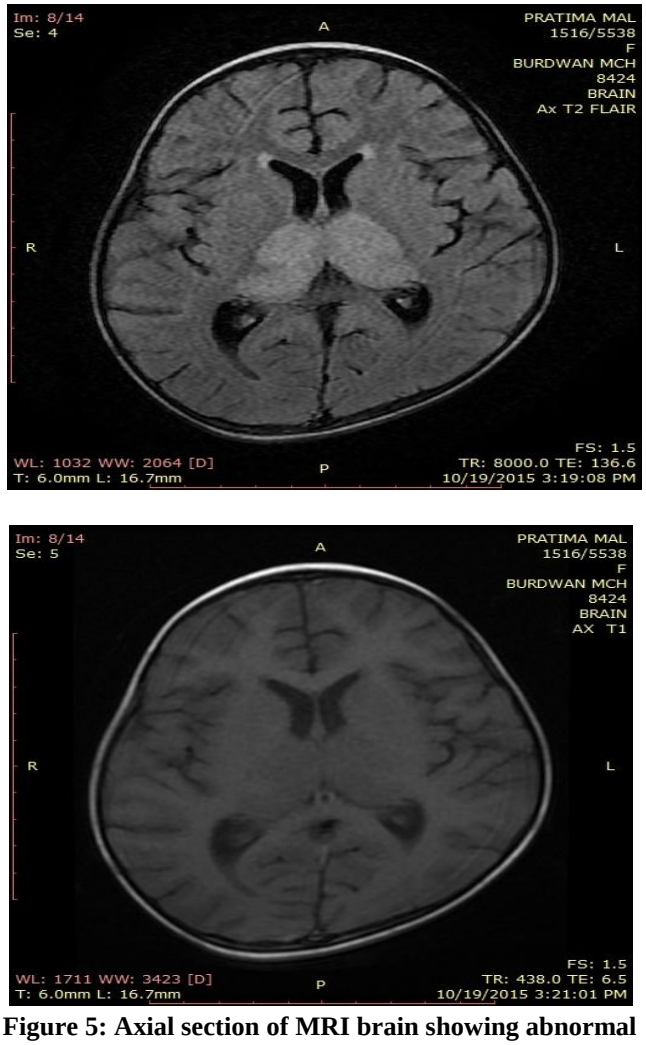

Figure 5: Axial section of MRI brain showing abnormal SI in bilateral thalamus
(Hyper intensity in FLAIR and hypo intensity in T1)

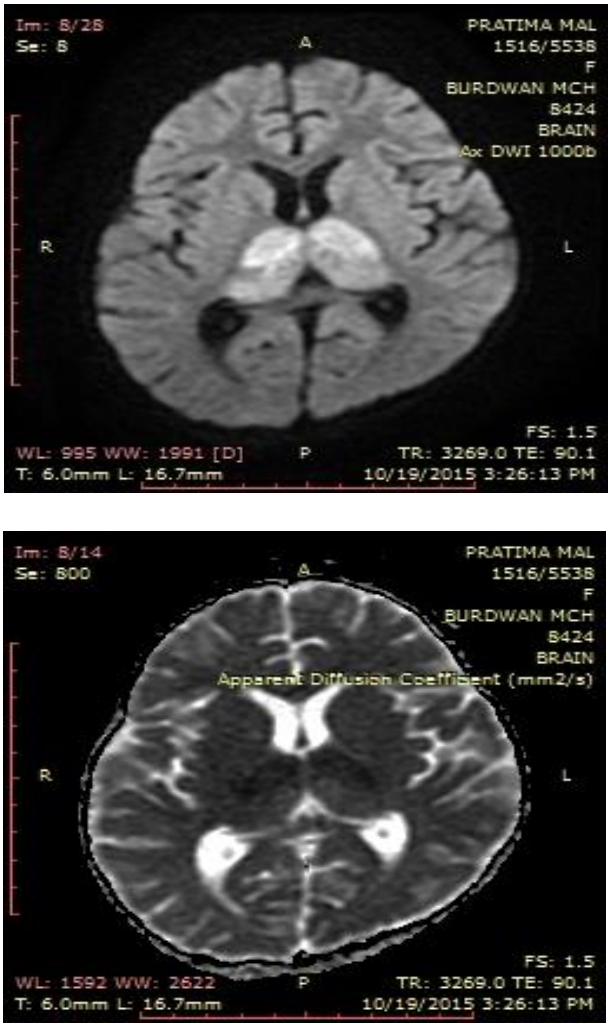

Figure 2: DWI sequence and ADC map showing true diffusion restriction in involved thalamus

References

[1]. Lobigs M, Diamond M. Feasibility of cross-protective vaccination against flaviviruses of the Japanese encephalitis serocomplex. *Expert Rev Vaccines.* 2012 Feb. 11(2):177-87.

[2]. Solomon T, Ni H, Beasley DW, Ekkelenkamp M, Cardosa MJ, Barrett AD. Origin and Evolution of Japanese Encephalitis Virus in Southeast Asia. *J Virol*. 2003 Mar. 77(5): 3091-8.

[3]. Burke DS, Lorsomrudee W, Leake CJ, Hoke CH, Nisalak A, *et al*. Fatal outcome in Japanese encephalitis. *Am J Trop Med Hyg.* 1985; 34:1203–1210.

[4]. King NJ, Getts DR, Getts MT, Rana S, Shrestha B, *et al*. Immunopathology of flavivirus infections. *Immunol Cell Biol.* 2007; 85:33–42.

[5]. Mathur A, Kulshreshtha R, Chaturvedi UC. Evidence for latency of Japanese encephalitis virus in T lymphocytes. *J Gen Virol.* 1989; 70(Pt 2):461–465.

[6]. Rios M, Zhang MJ, Grinev A, Srinivasan K, Daniel S, *et al*. Monocytes-macrophages are a potential target in human infection with West Nile virus through blood transfusion. *Transfusion.* 2006; 46:659–667.

[7]. Hunsperger EA, Roehrig JT. Temporal analyses of the neuropathogenesis of a West Nile virus infection in mice. *J Neurovirol.* 2006; 12:129–139.

[8]. Briese T, Jia XY, Huang C, Grady LJ, Lipkin WI. Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet.* 1999; 354:1261–1262.

[9]. Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, *et al*. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. *Science.* 1999; 286:2333–2337.

[10]. Mishra MK, Basu A. Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. *J Neurochem.* 2008; 105:1582–1595.

[11]. Handique SK, Das RR, Barman K, Medhi N *et al*. Temporal lobe involvement in Japanese encephalitis: problemsin differential diagnosis. *AJNR Am J Neuroradiol*, 2006 May; 27(5):1027-31.

[12]. Mehra S, Garga UC. Role of imaging in herpes and Japanese encephalitis- Two cases and review of literature. *JIACM* 2012;13(4):338-43.

[13]. Shoji H, Kida H, Hino H, Matsuura S, Kojima K, Abe T, Utsunomiya H, Okada Y, Nakamura Y, Okudera T. Magnetic resonance imaging findings in Japanese encephalitis: white matter lesions. *J Neuroimag* 1994; 4:206–211. DOI: 10.1111/jon199444206

[14]. Kumar S, Misra UK, Kalita J, Salwani V, Gupta RK, Gujral R. MRI in Japanese encephalitis. *Neuroradiology* 1997 Mar; 39(3):180-4

[15]. Kalita, J *et al*. Comparison of CT scan and MRI findings in the diagnosis of Japanese encephalitis. *Journal of the Neurological Sciences* 2000; 174(1): 3-8.