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Extent of disability among paediatric Japanese encephalitis survivors and predictors of poor outcome: a retrospective cohort study in North India

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ABSTRACT

Objective To determine the Japanese encephalitis (JE)-associated long-term functional and neurological outcomes, the extent of reduced social participation and predictors of poor outcomes among paediatric JE survivors.

Design A retrospective cohort study.

Setting Laboratory-confirmed JE-positive paediatric cases (<16 years of age) hospitalised at the paediatric ward of Baba Raghav Das Medical College, Gorakhpur, India, between 1 January 2017 and 31 December 2017, were followed up after 6–12 months of hospital discharge.

Participants 126 patients were included in the study; median age was 7.5 years (range: 1.5–15 years), and 74 (58.73%) were male.

Outcome measures Functional outcome defined by Liverpool Outcome Score (LOS) dichotomised into poor (LOS=1–2) and good (LOS=3–5) outcome groups compared for demographic, clinical and biochemical parameters for prognostic factors of poor outcomes. Social participation of patients scaled on Child and Adolescent Scale of Participation score 2–5.

Results About 94 of 126 (74.6%) children developed neurological sequelae at different levels of severity. Age-expected social participation was compromised in 90 out of 118 children. In multivariate logistic regression analysis, a combination of parameters, JE unvaccinated status (OR: 61.03, 95% CI (14.10 to 264); p<0.001), low Glasgow Coma Score (GCS) at admission (≤8) (OR: 8.6, 95% CI (1.3 to 57.1); p=0.026), malnutrition (OR: 13.56, 95% CI (2.77 to 66.46); p=0.001) and requirement of endotracheal intubation (OR: 5.43, 95% CI (1.20 to 24.44); p=0.027) statistically significantly predicted the poor outcome with 77.8% sensitivity and 94.6% specificity. The goodness-of-fit test showed that the model fit well (Hosmer-Lemeshow goodness-of-fit test) (χ^2=3.13, p=0.988), and area under the receiver operating characteristic curve was 0.950.

Conclusion This study estimates the burden of JE-presenting post-discharge deaths (15.4%) and disability (63.08%). Those who did not receive JE vaccine, were suffering from malnutrition, had GCS ≤8 at admission and required endotracheal intubation had poorer outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study used prevalidated questionnaire tools, that is, the Liverpool Outcome Score and Child and Adolescent Scale of Participation to assess the patients.
⇒ There were no missing data in the data sets for imputation.
⇒ However, this study has been conducted at a single-centre setting and with a limited sample size.

INTRODUCTION

Japanese encephalitis virus (JEV) causes a spectrum of functional and neurological impairment with significant morbidity and mortality.[1] In India, Japanese encephalitis (JE) is principally a disease of children aged less than 15 years[2] with a reported case fatality rate of 20%–30%.**3** Among patients with JE, deaths are reported in 30%–35% patients, while long-term neurological impairment is reported in 22%–94% of the survivors. Since 1978, Uttar Pradesh (UP) state of India has been an epicentre for seasonal outbreaks of acute encephalitis syndrome (AES) having JE as a major aetiology.[4] However, JE vaccination caused significant decline in JE incidence but sporadic cases still occur in the region.[4] During the year 2017, UP reported 693 JE cases and 93 deaths, out of which 299 (43.4%) JE cases and 66 (71%) deaths were from the eastern part of UP.[5] A significant proportion of JE disease burdens is caused by the long-term sequelae of the disease.[6] These sequelae are in the form of functional disability, neurological deficits and cognitive behavioural deficits that severely impact the social participation of survivors.[7] Guidelines for JE management emphasise on targeted supportive treatment, as there is no effective

antiviral medication against JEV.[8] The factors responsible for worse outcomes in JE may be amenable to timely treatment and can provide a framework for guiding decision-making, and targeted preventive strategies lead to improvement of patient prognosis as well as quality of life. Identifying these factors and rehabilitation needs in JE-endemic regions is imperative. Understanding the predictors of poor outcome in recovered paediatric patients with JE is necessary for planning the management effectively. In the present study, JE-associated long-term neurological and functional outcomes and the extent of reduced social participation among recovered children were determined. Patients' demographic, clinical, biochemical and sequelae data were analysed for predictors of poor outcomes.

METHODS

Study design

The study was conducted retrospectively, involving a cohort of children (aged ≤16 years) hospitalised in the paediatric ward of Baba Raghav Das Medical College (BRDMC), Gorakhpur with laboratory-confirmed JE between January 2017 and December 2017. Patients with JE were screened from the AES line list generated by the Regional Medical Research Centre, Gorakhpur, UP of Indian Council of Medical Research. Details of the patients' clinical history, routine biochemical findings and reports on aetiological investigations performed on cerebrospinal fluid/blood collected during discharge were also taken from the hospital records.

Case definitions

AES: a person of any age, at any time of the year, with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma or inability to talk) and/or new onset of seizures (excluding simple febrile seizure).[8]

JE-AES: a case that meets the clinical case definition of AES and laboratory confirmed as JE.[8]

Inclusion and exclusion criteria

Patients aged ≤16 years diagnosed with JE-AES from the AES line list were included in the study. Patients who denied consent, were not present at >2 times home visits, and those with no contact information or address were excluded in the study.

Patient follow-up, disability assessment and neurological examinations

The participating children were followed up between 6 and 12 months after discharge from the hospital (median duration 7 months, IQR 6–8). Their functional ability and social participation were assessed using standard tools, that is, the Liverpool Outcome Score (LOS 1–5)[9] and Child and Adolescent Scale of Participation (CASP 2–5) scores.[10] Motor and cranial neuron deficits were also recorded.

Statistical analysis

Patients were divided into two groups based on LOS, that is, 'poor outcome group' (LOS=1, 2) and 'better outcome group' (LOS=3, 4 and 5). Two groups were compared for demographic, clinical, biochemical and sequelae data. Mean, median and SD were calculated for continuous variables. Normally distributed data were analysed using Student's t-test or Mann-Whitney U tests, whichever was applicable. χ^2 test was used for categorical data. Statistically significant parameters whose p values were <0.05 in the univariate analysis were processed for predictive modelling using multivariate logistic regression analysis. Children who died post-discharge (scored 1 on LOS) were included in the outcome analysis. The Hosmer-Lemeshow goodness-of-fit test was used to assess fitness of predictive model. No missing data fields were found in variables. Sensitivity and specificity of the predictive model were determined, and performance of the model was assessed by constructing receiver operating characteristic curve. Area under the curve was determined. STATA V.13 software (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Patient characteristics

A total of 262 paediatric JE cases were hospitalised during 2017, of which 66 (25.2%) died during acute hospitalisation. Among the 196 (74.8%) discharged patients, 23 (11.7%) children died after hospital discharge (figure 1) due to severe complications (scored 1 on LOS). A total of 126 of 196 (64.3%) patients who fulfilled the inclusion criteria were assessed further; the median age was 7.5 years (range: 1.5–15 years), and 74 (58.73%) were male. The median duration between hospitalisation date (onset date) and follow-up/assessment date was 7 months (IQR 6–8).

Extent of disability, social behaviour and neurological findings

A total of 94 of 149 (63.08%) children developed neurological sequelae (scored 2–4 on LOS), while 32 (21.5%) recovered completely (scored 5 on LOS) (table 1). Age-expected social participation was compromised in 90 of 118 children (scored 2–4 on CASP) (table 1). Behavioural abnormality and aggressiveness were the most prominent features of neurological sequelae documented in 74.6% of children (table 2). Excessive salivation (16.7%) and squinting (26.9%) with weak eyesight (9.35%) and intermittent headache (10.1%) were also documented prominently (table 2). Motor examinations observed monoparesis in 5.5% children, while hemiparesis and quadriparesis were observed in 4% and 1.6% children, respectively (table 2).

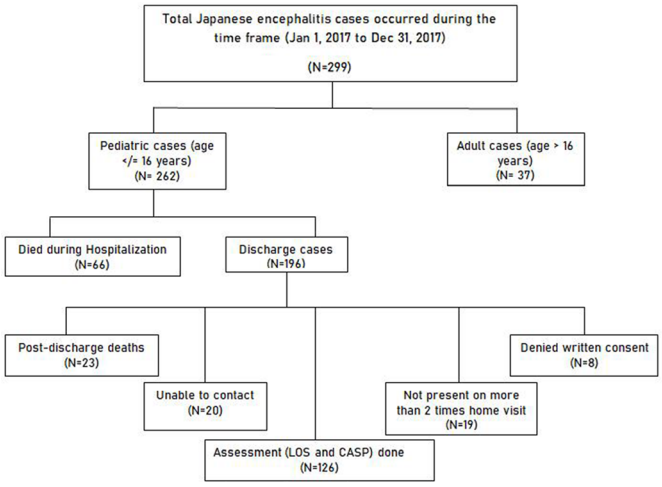

Figure 1 Flow chart of screening process and recruitment of patients for LOS and CASP assessment. One hundred ninety-six of the 299 patients screened from the line list of encephalitis cases hospitalised in the medicine and paediatric ward of Baba Raghav Das Medical College (BRDMC) met the inclusion criteria and were recruited for the study. One hundred twenty-six patients were assessed for disability and level of social participation using standardised questionnaire tools LOS (Liverpool Outcome Score) and CASP (Child and Adolescent School of Participation). Clinical, biochemical and laboratory data of these patients were taken from the hospital record of BRDMC.

Predictors of a poor outcome

Of the surviving patients, 113 (75.8%) had a better outcome (LOS score 3–5) and 36 (24.2%) had a poor outcome (LOS score 1–2). Patients who died post-hospital discharge scored 1 on LOS (table 1). Both poor and better outcome groups were compared for predictors of the outcome. There were no missing data for imputation. In the univariate analysis, non-immunisation against JE (p<0.001), malnutrition (measured as per WHO standards by measuring weight for height, weight for age, height for age and body mass index (BMI))[11] (p=0.027), requirement of endotracheal intubation (p=0.013), inotrope support (p=0.013), Glasgow Coma Score (GCS) less than and equal to 8 (p=0.001), vomiting (p= 0.009), altered sensorium (defined as limitations in the brain's ability to receive, process or interpret the sensory information[12] and detected using GCS) (p=0.006), multiple episodes (>1) of seizures (p=0.013), unconsciousness (p=0.001), extensor plantar (p=0.016), hypernatraemia (serum sodium >145 mmol/L) (p=0.019), hypotension (p=0.02) and anaemia (haemoglobin <80 g/L) (p=0.007) were found to be significantly associated with worst outcomes (table 3). All these parameters were taken to the predictive model by the multivariate logistic regression analysis. In the multivariate logistic regression analysis, a combination of parameters, JE unvaccinated status (OR: 61.02, 95% CI (14.10 to 264); p<0.001), low GCS at admission (≤8) (OR: 8.62, 95% CI (1.3 to 57.1); p=0.026), malnutrition (OR: 13.56, 95% CI (2.76 to 66.46); p=0.001) and requirement of endotracheal intubation (OR: 5.43, 95% CI (1.21 to 24.43); p=0.027) statistically significantly predicted a poor outcome (table 4) with 78% sensitivity and 94.6% specificity (table 5). The goodness-of-fit test showed that the model fit well (χ^2=3.13, p=0.988), and the area under the receiver operating characteristic curve was 0.950 (figure 2).

Table 2 Findings of neurological examinations

Neurological examinations	Number of patients (%)
Motor examination	
Quadriparesis	2 (1.6)
Hemiparesis	5 (4)
Monoparesis	7 (5.5)
Cranial nerve symptoms	
Squinting	34 (26.9)
Dysphagia	07 (5.5)
Excessive salivation	21 (16.7)
Slurring of speech	13 (10.3)
Cortical (cognitive symptoms)	
Behavioural disturbances	94 (74.6)

Table 1 Liverpool Outcome Score (LOS) and Child and Adolescent Scale of Participation (CASP) scores obtained by patients and their interpretation

LOS (N=14)			CASP (N=118)		
Score	No of patients (%)	Score interpretation	Score	No of patients (%)	Score interpretation
1	23 (15.4)	Death	–	–	–
2	13 (8.7)	Severe sequelae, impairing function sufficient to make patient dependent	2	14 (11.9)	Unable to participate
3	27 (18.1)	Moderate sequelae mildly affecting function, probably compatible with independent living	3	26 (22)	Very limited participation
4	54 (36.2)	Minor sequelae with no effect or only minor effect on physical function, or personality change, or on medication	4	50 (42.4)	Somewhat limited participation
5	32 (21.5)	Full recovery	5	28 (23.7)	Age-expected participation

Table 3 Univariate analysis of demographic characteristics, clinical features, biochemical parameters and sequelae data

Characteristics	Poor outcome group (LOS=1/2) N=36 (%)	Better outcome group (LOS=3/4/5) N=113 (%)	X^2	P value
Univariate analysis of demographic characteristics, clinical signs, symptoms and complications (n=149)				
Mean age	6.5 years	6.9 years	–	–
Gender			2.17	0.14
Male	15 (41.7)	63 (55.7)		
Female	21 (58.3)	50 (44.24)		
Locality				
Rural	35 (97.2)	107 (94.7)		
Urban	1 (2.8)	6 (5.3)		
Occupation of parents/guardian			0.0039	0.95
Daily wage labourer	26 (72.2)	81 (71.7)		
Other	10 (27.8)	32 (28.3)		
JE unvaccinated status	13 (36.1)	19 (16.8)	23.31	<0.001
Required hospitalisation for more than 15 days	16 (44.4)	10 (8.84)	3.5152	0.061
Malnutrition	33 (91.7)	62 (54.9)	4.87	0.027
Fever onset for >7 days	16 (44.4)	59 (52.2)	0.667	0.41
High-grade fever (>38°C)	21 (58.3)	73 (64.6)	0.46	0.49
Requirement of endotracheal intubation	9 (25)	16 (14.15)	6.17	0.013
Patient on anticonvulsant	31 (86.1)	93 (82.3)	0.209	0.647
Patient on inotropes (dopamine/dobutamine)	18 (50)	60 (53.1)	6.22	0.013
Vomiting	18 (50)	65 (57.5)	6.79	0.009
Headache	6 (16.6)	22 (19.5)	0.85	0.36
Altered sensorium	30 (83.3)	81 (71.7)	7.56	0.006
Multiple seizures (>1)	25 (69.4)	78 (69)	6.22	0.013
Rolling of eyeballs	26 (72.2)	82 (72.6)	3.70	0.054
Hypertonia	25 (69.4)	72 (63.7)	0.39	0.53
Extensor plantar	28 (77.8)	74 (65.5)	5.79	0.016
Hypotension (SBP <90 mm Hg/DBP <60 mm Hg)	15 (41.7)	68 (60.2)	5.45	0.02
Glasgow Coma Score ≤8	34 (94.4)	75 (66.4)	10.24	0.001
Unconsciousness	7 (19.4)	12 (10.6)	10.15	0.001
Anaemia (Hb ≤80 g/L)	10 (27.8)	11 (9.7)	7.34	0.007
Hypernatraemia (Na >145 mmol/L)	7 (19.4)	7 (6.2)	5.46	0.019
Alkaline phosphatase >147 IU/L	11 (30.5)	55 (48.7)	1.4111	0.235
Metabolic acidosis (pH <7.3)	7 (19.4)	18 (15.9)	5.96	0.056

DBP, diastolic blood pressure; Hb, haemoglobin; JE, Japanese encephalitis; LOS, Liverpool Outcome Score; Na, sodium; SBP, systolic blood pressure.

This predictive model have four effects: JE unvaccinated status (unvac), GCS ≤8 (gcs), malnutrition (mal) and endotracheal intubation (intub). The goodness-of-fit test suggests there are no gross deficiencies with the model. The small p value (<0.0001) for the logistic regression X^2 statistic implies that one or more effects in the model are important for predicting the probability of a poor outcome. The tests for parameters suggest that each effect in the model is significant at the 0.05 level (p<0.05). The equation for the given logistic regression predictive model is as follows:

Log (p^/1−p^)=−8.57+2.60mal+2.15gcs+4.11unvac+1.69intub

Where p^=estimated probability of a poor outcome.

DISCUSSION

In this study, we assessed the outcome among paediatric JE survivors after 6–12 months of hospital discharge. The aims of this study were to determine the extent of functional and social disabilities among children hospitalised with JE and to determine the factors that might be associated

Table 4 Multivariate logistic regression analysis of factors associated with poor outcome due to JE

Variable	OR (95% CI)	P value
JE unvaccinated status	61.03 (14.1 to 264)	<0.001
Malnutrition	13.56 (2.77 to 66.46)	0.001 (<0.05)
Glasgow Coma Score ≤8	8.6 (1.3 to 57.1)	0.026 (<0.05)
Requirement of endotracheal intubation	5.43 (1.20 to 24.44)	0.027 (<0.05)

JE, Japanese encephalitis.

with the poor outcome. Our results showed that 63.08% (N=94) of children developed neurological sequelae at different levels of severity, and 15.4% (N=23) of children died after hospital discharge at home. Among 94 children, 13 (8.7%) were found severely disabled at the time of follow-up, 27 (18.1%) were found moderately disabled and 54 (36.2%) had mild neurological sequelae mostly in the form of behavioural changes and aggressiveness. In addition, reduced social participation at home/school/community was observed in 76.2% (N=90) of children. Disabled patients who were further assessed for motor and cranial deficits showed gross motor involvement in the form of quadriparesis (1.6%), hemiparesis (4%) and monoparesis (5.5%). Behavioural abnormalities were the most frequently observed cognitive (cortical) symptoms reported in 74.6% (n=94) of patients. Squinting (one or both eyes) and excessive salivation were other most prominent cranial nerve symptoms observed in 26.9% (n=34) and 16.7% (n=21) of patients, respectively. The reason behind hypersalivation/excessive salivation in these patients was not studied; this might be due to neurological impairment or could be due to endotracheal intubation as patients in intubation for more than 48 hours could have long-term swallowing/oral intake difficulty.[13 14] Previous studies from China, Vietnam, Cambodia, Indonesia, Malaysia, Nepal and India determined the extent of disability among JE survivors and reported varied estimates of disability that range from 50% to 70% among paediatric JE survivors.[7 15–18] Nevertheless, the data from this study and other previous studies showed significant burden of JE in the form of disability. In our study, 32 (21.5%) children were found fully recovered and 28 (23.7%) children had age-expected social participation. Previous studies demonstrated that most changes

Table 5 Sensitivity and specificity of the logistic regression model

Sensitivity	Specificity	Positive predictive value	Negative predictive value
77.8%	94.6%	82.35%	92.9%

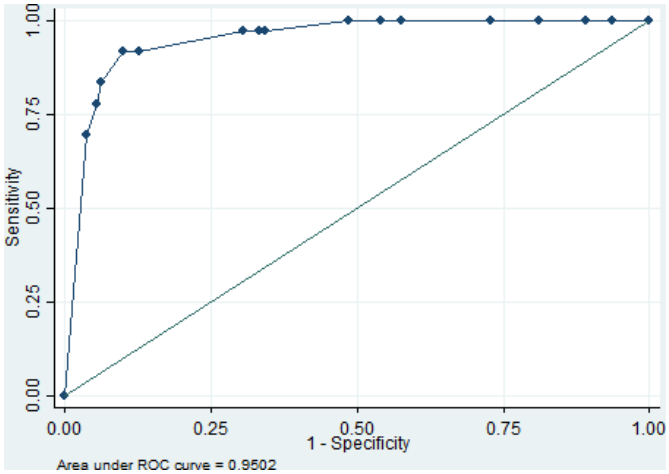

Figure 2 Receiver operating characteristic (ROC) curve for regression model and area under the curve.

(ie, improvement or deterioration) in JE-infected children occur soon after hospital discharge. About 75% of patients assessed between 3 and 6 months after hospital discharge had an identical status when assessed again at a later time.[7 17] Therefore, all children in this study were assessed at least 6 months after discharge from hospital to observe the long-term outcome. One or both parents of about 70% of children were daily wage labourers, which highlights the poor socioeconomic status of the family.

Another goal of this study was to determine the factors that might be associated with poor outcomes in JE survivors. We found that children who were non-vaccinated against JE had malnutrition, had low GCS (≤8) and required endotracheal intubation at the time of admission had a poor outcome after hospital discharge. As there are no specific antiviral medications for JE and symptomatic treatment is the only way to manage the severity caused by JE, this study shows the importance of JE vaccination. We suggest strengthening JE immunisation campaigns by creating awareness among communities and recommend checking of children at school entries for JE vaccination. Low GCS in patients objectively defines the extent of impaired consciousness among patients with brain injury or trauma.[19] The adverse effects of low GCS among patients with encephalitis are recorded earlier and are a well-established marker for a poor outcome in JE.[20 21] Our study also observed a significant association of low GCS (≤8) with a poor outcome in JE. As per the WHO definition, malnutrition is defined as imbalances (deficiency/excess) in intake of nutrients by a person and it is measured by weight for height, height for age, weight for age and BMI.[11] The current predictive model observed an association of malnutrition with a poor outcome, and previous studies also recorded the significant similar finding.[22] Endotracheal intubation requirement is highly suggestive of severity in patients, and a previous study reported this as a significant predictor of mortality among patients with encephalitis.[23] In the current study, we observed a significant association between requirement of endotracheal intubation and poor outcomes.

We additionally asked the disabled patients' guardians about how frequently they take their child to rehabilitation centres of BRDMC, and most of the families complained that the rehabilitation centre (Child Rehabilitation Centre, BRDMC) is so distant that they cannot afford and manage to take their disabled child this far for therapy on a regular basis. This study highlighted the need to strengthen JE vaccination coverage, framing of policies for rehabilitation services for the disabled and interventional programmes to improve nutritional status of children in JE-endemic regions. We observed squinting in a significant number of children (26.9%); hence, a thorough ophthalmological examination of patients with JE for any ophthalmic complications is recommended at discharge and follow-up.

There are some limitations of this study as this study was conducted at a single centre and with a limited sample size, though this is the only tertiary care centre that catered to patients from this region. Another limitation of this study is that responses to the questions might be influenced by the awareness and knowledge of parents. The investigators suspect that sometimes parents deny disclosing their child's abnormalities because of fear of discrimination in the society. We managed to assess 76% of patients with JE discharged from hospital in a year and there is a possibility that results could have been varied if all had been assessed. A further prospective study is needed to determine whether proper management of prognostic factors in the present study, that is, low GCS, malnutrition and requirement of endotracheal intubation could improve the outcome in patients with JE.

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Contributors Study concept and design—VPB, HD and NS. Data acquisition—NS, HD and VPB. Analysis and interpretation of data—RY, NS, AD and VPB. Drafting of the manuscript—NS, VPB, AD, HD and MM. Critical revision of the manuscript for important intellectual content—VPB, AD, MM, HD and RK. Statistical analysis—RY, NS and AD. overall guarantor-HD, NS

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The ICMR-National Institute of Virology, Pune Institutional Human Ethics Committee approved this study (ref ID: NIV/IHEC/2016/D-310). Informed consent was obtained at follow-up from each child's parent or legal guardian.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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