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Prevalence & clinical outcome of autoimmune encephalitis *versus* viral encephalitis in children with acute encephalitis syndrome: A prospective observational study

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***Background & objectives*: Acute encephalitic syndrome (AES), encompasses a wide spectrum of potential causes, clinical presentations, and outcomes. While infectious encephalitis is generally considered more prevalent, autoimmune encephalitis is emerging as a significant aetiology. Neuronal autoantibodies have been identified independently or in association with acute viral encephalitis. The primary objective of this study was to ascertain the prevalence and clinical manifestation of autoimmune encephalitis as well as of coexisting viral markers in children with AES.**

***Methods*: This study was a prospective observational investigation conducted in a hospital setting. It involved enrolling children with AES who were admitted to specific tertiary hospitals. Children were subjected to examinations to detect the presence of viral markers and neuronal autoantibodies in both their blood and cerebrospinal fluid (CSF). All the participants received treatment based on established guidelines and was followed for six months for outcome assessment.**

***Results*: During the study period, 867 children with AES were examined. Among these cases, 37 children (4.2%) were diagnosed with autoimmune encephalitis, and all of them tested positive for anti-NMDAR (N-methyl-D-aspartate receptor) antibodies. Evidence of viral infection was seen in 409 (47.1%) of cases, out of which nearly 254 (29.2%) children had detectable HSV IgM antibodies. Among the 37 children with autoimmune encephalitis, 25 (67.5%) had evidence of a viral trigger, with eight of them tested positive for HSV IgM antibodies. The clinical presentation of autoimmune-associated AES was similar to those with viral aetiology.**

***Interpretation & conclusions*: Autoimmune encephalitis triggered by neurotropic (HSV) viral infection was more prevalent in this study than in the earlier reports. Typically, these children show positive responses to immunosuppressive treatments if administered promptly. It is hence advisable to assess children who exhibit behavioural issues and movement disorders for possible autoimmune encephalitis.**

Key words Acute encephalitis syndrome (AES) - anti-NMDAR encephalitis - autoimmune encephalitis - children - immune mediated encephalitis - viral encephalitis

Clinically, acute encephalitis syndrome (AES) was typically defined as a child presenting with acute onset of fever and change in the mental status that may include disorientation, confusion, difficulty to talk, or command/or new onset of seizures (simple febrile seizures excluded)[1]. Viral encephalitis is reportedly an important cause of morbidity and mortality in children with AES. This may be sporadic such as herpes simplex encephalitis (HSE), or an epidemic such as Japanese B encephalitis (JE). However, the treating physicians can often feels restricted by the lack of availability of diagnostic testing for most of these agents.

Autoimmune encephalitis (AIE) is recognized as one of the leading causes of non-infectious acute encephalitis. In northern Europe, it is estimated that immune-mediated encephalitis accounts for approximately 20 per cent of all encephalitis cases[2]. However, there is a paucity of literature on this topic from Southeast Asia including India, with the existing information primarily comprising retrospective case series[3-5]. Although cases of concurrent viral encephalitis and AIE have been documented in literature, these instances are predominantly observed in adults[6]. Various viruses, including herpes viruses such as herpes simplex virus 1 (HSV-1) or HSV-2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus, and human herpes virus 6 (HHV 6) have been associated with AIE. The spectrum of anti-neuronal antibodies encountered in these cases includes N-methyl-D-aspartate (NMDA), γ-aminobutyric acid A and B (GABAAR, GABABR), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), leucine-rich glioma inactivated-1 (LGI1), dipeptidyl-peptidase-like protein 6 (DPPX), contact in-associated protein-like 2 (Caspr2), and others[7,8]. Among these, anti-NMDAR encephalitis is the most frequently reported form of AIE in the literature and is more common in the paediatric age group than in adults.

Previously published data from the California Encephalitis project indicate that approximately 30 per cent of cases of viral encephalitis are associated with autoimmune antibodies[6]. Furthermore, there has been no systematic evaluation of the outcomes of these coexisting conditions. There is a dearth of data from India and other tropical countries regarding the co-occurrence of viral and AIE, mainly due to the fact that routine evaluation is not a standard practise. Only two anecdotal case reports from India has suggested such associations, with some cases showing improved outcomes[9,10]. The presence of AIE alongside viral encephalitis is more likely to lead to long-term complications, as these individuals are neither screened for autoantibodies nor receive treatment. The primary objective of the current study was to determine the prevalence of coexisting neuronal autoantibodies in children diagnosed with acute viral encephalitis and documenting the clinical manifestation and outcome of AIE.

Material & Methods

This was a prospective observational multisite hospital-based study carried out in children with acute encephalitic syndrome. These children were between the age group of six months to 14 yr and admitted to five large tertiary care hospitals in two States namely, Odisha and Uttar Pradesh (UP) in India documenting high burden of AES cases. Children with AES as defined by the National Vector born disease control programme (NVBDCP, India; *http://www.nvbdcp.gov.in/Doc/AES%20guidelines.pdf*) were included in the study. Children with an alternate diagnosis like bacterial or tubercular encephalitis, cerebral malaria, malignancy or metabolic encephalopathy were excluded from the study.

Children with AES who were admitted to the designated tertiary study hospitals in the two States were consecutively included in the study from October 2019 to October 2022. Following admission, comprehensive personal history and clinical examination details were documented and subjected to laboratory analysis in accordance with the hospital's AES management protocol. Those meeting the specified inclusion and exclusion criteria were enrolled with parental consent. A 2 ml CSF sample and a 2 ml blood sample in a red-top vacutainer were collected at the participating study centres and securely transported to the nodal centres [All India Institute of Medical Sciences (AIIMS), Bhubaneswar/ King George's Medical University (KGMU), Lucknow] for analysis with appropriate precautions. Comprehensive baseline, clinical, and laboratory assessments were documented. The study was conducted following GCP guidelines with approval from the institute ethics committee (IEC) from both the Institutes.

The testing of viral markers and autoantibodies was done in CSF and serum samples. The investigation of viral markers encompassed viruses, such as HSV-1, HSV-2, VZV, Japanese encephalitis virus, measles, enteroviruses, EBV, cytomegalovirus, parvovirus B19, enterovirus, dengue and HHV-6. Seromolecular

Table I. Aetiology of AES among enrolled children (n=867) as evident by viral and neuronal antibodies from serum and/or CSF

Parameters	Odisha (n=511), n (%)	UP (n=356), n (%)	Total (n=867), n (%)
Viral encephalitis (neuronal antibody negative)	248 (48.5)	161 (45.1)	409 (47.1)
Anti-NMDAR encephalitis (all neuronal antibody positive)	32 (6.2)	5 (1.4)	37 (4.3)
Both viral & anti-NMDAR encephalitis (viral & neuronal antibody positive for both)	20 (3.9)	5 (1.4)	25 (2.9)

AES, acute encephalitis syndrome; UP, Uttar Pradesh; CSF, cerebrospinal fluid

investigation included detection of antibodies and PCR assays for DNA/RNA depending on the specific virus type[11]. We also estimated the level of IgM antibodies for the viruses mentioned above. However, HSV IgG was only done for those children who were positive for anti-NMDAR antibody.

Autoantibodies were screened for NMDA-R, AMPA1, AMPA2, CASPR, LGI-1, and GABAB receptor was conducted on (B1, B2). Testing of autoantibodies was done by indirect immunofluorescence (IIF) assay. These assays transfected cell lines for qualitative determination of human antibodies against glutamate and VGKC receptors in serum/CSF by using Cell Based Assay (CBA) using a commercially available kit (Euroimmune, Germany). The sensitivity and specificity of CBAs using serum or CSF have been well established[12-15]. Details of treatment received during hospital stay were recorded in a predesigned proforma. Clinical status at discharge was documented and subsequently, the patients were followed on an outpatient basis at one, three and six months from the date of onset of illness.

Sample size: Assuming 10 per cent prevalence of autoantibodies among viral AES cases, the sample size of 144 was calculated to be adequate with 95% confidence interval (CI) and five per cent absolute precision. Assuming the minimum prevalence of viral aetiology to be around 20 per cent among AES cases to get 144 cases of viral AES, we a total of 720 (5*144=720) AES cases were to be enrolled in this study. As it was also planned to follow the cases for six months to adjust loss to follow up of around 10 per cent, a total sample size of 800 was considered for the study. This sample was distributed into 400 each for Odisha and Uttar Pradesh sites (Formula n= Z^2 p (1-p)/ d^2; used for calculating sample size).

Statistical analysis: Statistical analysis was carried out using the STATA 19 software package. Continuous data were expressed as the mean along with the standard deviation, while categorical variables were presented as proportions and ratios. To assess differences between the two groups, the independent sample t-test or Mann-Whitney U tests were used for continuous variables and chi-square test or Fischer's Exact test was used for categorical variables wherever suitable. Odds ratio was calculated using binomial logistic regression model to look for an association with the type of encephalitis (NMDA *vs.* HSV) and outcomes. A *P* value (two-sided) below 0.05 was considered as indicative of statistical significance.

Results

Throughout the study period, a total of 867 children with autoimmune and viral aetiology of AES were enrolled at the two designated study centres, with 511 children from Odisha and 356 children from UP. Of these, 37 children (4.2%) received a diagnosis of AIE, and all of them tested positive for anti-NMDA receptor antibodies. While we conducted screenings for other antibodies, including AMPA1, AMPA2, CASPR, LGI-1, and GABAB receptor (GABAB1, B2), none of these antibodies were detected. It's worth noting that the Odisha site had 32 children who tested positive for anti-NMDA receptor antibodies, whereas the Uttar Pradesh site had only five such cases (Table I).

Within the AES cases, 409 (47.1%) had evidence of a viral infection, of which 254 (29.2%) tested positive for HSV IgM antibodies. In children with AIE, 30 (81%) displayed the presence of anti-NMDA autoantibodies in their CSF, while 6 (16.3%) had them in their serum, and 1 (2.7%) exhibited in both. In instances of non-autoimmune encephalitis, HSV emerged as the most commonly associated virus. HSV IgM antibodies were detected in nearly 254 (29.2%) children in the overall study sample. Among children with AIE, a viral trigger was present in 25 (67.5%) cases. Within this group, eight tested positive for HSV IgM antibodies, 12 for HSV IgG antibodies, and one child had both antibodies identified. Additionally,

Table II. Seromolecular markers of viral infection associated with AES with a comparison between NMDA encephalitis and NMDA negative viral encephalitis group

Parameter	NMDA encephalitis* (n=37)	Viral encephalitis** (n=409), n (%)	Total AES (n=867), n (%)
Serum HSV1 IgM	9 (21.6)	246 (60.1)	254 (29.2)
Serum HSV1 IgG	12 (32.4)	NA	NA
Serum HSV II IgM	0	6 (1.5)	6 (0.7)
Serum VZV IgM	0	4 (1)	4 (0.5)
Serum JE IgM	1 (2.7)	7 (1.7)	8 (1)
CSF JE IgM	1 (2.7)	18 (4.4)	19 (2.2)
Serum Measles	0	2 (0.5)	2 (0.2)
Serum VZV	0	2 (0.5)	2 (0.2)
CSF VZV	0	1 (0.2)	1 (0.1)
CSF EBV	0	8 (1.9)	8 (1)
Serum HCMV	0	3 (0.7)	3 (0.3)
CSF HCMV	0	13 (3.1)	13 (1.5)
CSF HHV6	0	4 (1)	4 (0.5)
CSF HADV	0	11 (2.7)	11 (1.2)
Serum HHV7	0	1 (0.2)	1 (0.1)
CSF HHV7	0	15 (3.7)	15 (1.7)
Serum parvo B19	0	10 (2.5)	10 (1.1)
CSF parvo B19	2 (5.4)	37 (9.1)	39 (4.5)
Enterovirus CSF	0	0	0
Serum Dengue IgM	0	21 (5.1)	21 (2.4)

*Shows coexistence of markers of viral infection/viral trigger in children with a neuronal autoantibody-positive
**Show distribution of viral markers in those children diagnosed as viral encephalitis who are negative for autoantibody-positive
VZV, varicella-zoster virus; HCMV, human cytomegalovirus; HHV, human herpes virus; HADV, human adeno virus; JE, Japanese encephalitis; NDMA, N-methyl-D-aspartate

two children were positive for Japanese encephalitis IgM and parvovirus IgM antibodies within their CSF. We conducted a comparative analysis of the clinical characteristics and outcomes of children with HSV-associated encephalitis and those with AIE (Table II).

Demographic characteristics of NMDA vs HSV encephalitis: The median age of presentation of anti-NMDAR encephalitis was 7 (4-11) yr, while that of HSV encephalitis was 6 (3-9) yr. Both boys and girls were affected equally in both groups, indicating no gender preference. In terms of the time, it took from the onset of symptoms to a diagnosis of AIE, the median duration was 20 (12-32) days. In contrast, children with HSV encephalitis had a significantly shorter median duration of 8 (5-12) days from the onset of illness to diagnosis (Table III). There is a significantly higher proportion of AIE cases from the State of Odisha located on the eastern coast of India as compared to that of UP, a northern State of India.

Clinical features NMDA vs. HSV encephalitis: The majority of children presented with symptoms such as seizures (80%), altered consciousness (70%), and fever (70%) among children with AIE. Headaches were reported by 16 per cent of children, while behavioural abnormalities were present in 13 per cent of cases. Abnormal movements were observed in 10 children (27%). The clinical presentation of HSV encephalitis didn't differ significantly from AIE, except for the fact that skin rash was more frequently associated with HSV encephalitis. In contrast, behavioural changes and abnormal movements were more commonly observed in cases of anti-NMDAR encephalitis (Table III).

Cytological and biochemical changes in CSF: Nearly all the children underwent a lumbar puncture upon admission. In the anti-NMDAR encephalitis group, the mean total cell count in CSF was 9 (±2) cells, whereas in HSV encephalitis, it was 18 (±4) cells, and the predominant cell type was lymphocytic in both groups.

Table III. Comparison of demographic and clinic-biochemical parameters between anti-NMDA encephalitis and HSV encephalitis group

Parameter	NMDA encephalitis* (n=37), n (%)	HSV encephalitis** (n=246), n (%)	*P* value
Age (yr)	7 (4-11)	6 (3-9)	0.12
Duration in days before testing [Median (IQR)]	20 (12-32)	8 (5-12)	<0.05
Gender			
Girls	21 (56.7)	117 (47.5)	0.29
Boys	16 (43.3)	129 (52.5)	
Clinical presentation			
Fever	24 (64.8)	222 (90.2)	<0.05
Headache	5 (13.5)	45 (18.2)	0.47
Vomiting	12 (32.4)	119 (48.3)	0.07
Seizure	28 (75.6)	180 (73.1)	0.74
Altered sensorium	27 (72.9)	191 (77.6)	0.52
Skin rash	0	21 (8.5)	0.08
Delirium	0	9 (3.6)	0.61
Comatose	0	8 (3.2)	0.6
Confusion	11 (35)	59 (23.9)	0.54
Behavioural changes	7 (18.9)	21 (8.5)	0.07
Lab investigation			
CSF study			
Total cell	5 (2-10)	5 (2-10)	0.97
PMN (%)	10 (0-27)	10 (0-27)	0.81
Lymphocyte (%)	50 (0-80)	70 (0-90)	0.42
Sugar	62 (51-75)	63 (50-80)	0.41
Protein	38 (24-75)	64 (32-100)	0.03

*Those showing anti-NMDAR antibody with or without a coexisting viral trigger
**Those having a viral marker positivity but without any anti-neuronal antibody
IQR, interquartile range

In children with HSV encephalitis, the CSF protein levels were notably higher (Table III).

Treatment received during hospital stay: All the children were managed as per treatment standard AES protocol which included empirical antibiotics (ceftriaxone±vancomycin), antiviral (acyclovir) along with doxycycline if lab parameters suggested scrub meningitis. Continuation and duration of antibiotics and/or antiviral were decided by laboratory confirmation of the aetiology. Other than antibiotics and the antiviral, supportive management was given for elevated intracranial tension and seizure. In anti-NMDAR encephalitis group three and in HSV encephalitis group 13 required mechanical ventilation. Out of 37 children with anti-NMDAR encephalitis, 31 (83.8%) children received pulse methylprednisolone for three days at a dose of 15 mg/kg followed by oral steroids for a period of three months with gradual tapering dose while the rest six did not. Five (13.5%) children received both IVIg and steroids. The mean duration of hospital stay was 21 (6-64) days.

Outcome at discharge: Of the children with NMDA encephalitis, 32 (86.5%) were discharged from the hospital, and there were 3 (8.1%) deaths during their hospital stay. Upon discharge, 11 (29.7%) had achieved complete recovery without any neurological after effects, while 21 (56.7%) exhibited neurological sequelae in the form of altered consciousness, behavioural problems, and movement disorders. In contrast, 207 (84.1%) children with HSV encephalitis were discharged, and 35 (14.2%) deaths occurred during their hospitalization. Complete recovery was observed in 159 (64.6%) of these children, and 48 (19.5%) were discharged with neurological sequelae (Table IV).

Table IV. Outcome of children with anti-NMDA encephalitis *vs.* HSV encephalitis during hospital stay and six-month follow up from the onset of illness

Parameter	NMDA encephalitis* (n=37), n (%)	HSV encephalitis** (n=246), n (%)	Odd ratio (95% CI)	*P* value
Outcome				
Discharged from hospital	32 (86.4)	207 (84.1)		
Death	3 (8.1)	35 (14.2)	1.8 (0.52-6.21)	0.35
Left against medical advice	2 (5.4)	4 (1.6)	0.3 (0.05-1.7)	0.18
Condition at discharge				
Complete recovery	11 (29.7)	159 (64.6)		
Discharge with sequelae	21 (56.7)	48 (19.5)	0.15 (0.07-0.35)	<0.05
Outcome at 6 month follow up				
Complete recovery	22 (59.4)	169 (68.7)		
Sequelae (altered sensorium or behavioural abnormality)	10 (27)	37 (15.04)	0.48 (0.21-1.1)	0.08
Total death	5 (13.5)	40 (16.2)	1.04 (0.37-2.91)	0.93

*Those showing anti-NMDAR antibody with or without a coexisting viral trigger
**Those having a viral marker positivity but without any anti-neuronal antibody

Follow up at six months: Complete recovery was documented in 22 (59.4%) children, with no recurrence of symptoms. Three (8.1%) children remained in a state of altered consciousness, necessitating home-based nursing care, including nasogastric feeds and physiotherapy. Additionally, 7 (18.9%) children continued to experience behavioural problems and learning disabilities, despite improvements in consciousness. There were two more deaths observed during the six-month follow up period in children with anti-NMDAR encephalitis whereas five more deaths in children with HSV encephalitis. However, in HSV encephalitis group, 169 (68.7%) had complete recovery at six-month follow up. Behavioural abnormality was observed in higher proportion of children with anti-NMDAR encephalitis as compared to HSV encephalitis (Table IV).

Discussion

Autoimmune encephalitis is one of the significant causes of AES in the paediatric age group which has been detected increasingly over the last two decades[5]. Anti-NMDR encephalitis is the most common variant of AIE in the paediatric age group. Post-infectious AIE has been reported in the paediatric age groups in a few series. However, the reports are largely restricted to Western countries[16,17].

In the current study, of the children who had AES, 37 (4.2%) children tested positive for anti-NMDAR antibodies. The estimated prevalence of AIE was 13.7 per million population as reported by Dubey *et al*[18] in a retrospective study including both children and adults where the prevalence of specific neuronal antibodies against NMDA receptor was reported to be 0.6/100,000[18]. A retrospective study from Hong Kong by Peery *et al*[19] reported an estimated prevalence of 2.2 per million among children. Among seropositive AIE in children, NMDA encephalitis constitutes almost four per cent which is the most common. There was not much data available regarding the exact prevalence of AIE in children and adults from India. In a systematic review of cases of NMDA encephalitis, the majority were of age group below 18 yr (81.5%) as compared to adults. In the current study, we observed a similar prevalence of 4.2 per cent in our cohort[20].

In this study, 81 per cent of CSI samples tested positive for anti-NMDAR antibodies whereas in serum it was 16.3 per cent. Similar results of higher sensitivity for CSF neuronal antibodies ranging from 98.5-100 per cent have been reported in multiple studies[14,21]. Chowdhury *et al*[20] reported a CSF positivity of 73 per cent in children in a systematic review from India[20].

HSV infection is known to trigger anti-NMDAR encephalitis both in children and adults. Twenty one (56.7%) children with anti-NMDAR encephalitis had either HSV IgM or IgG positive whereas two had antibodies positive for JE and Parvo B19. HSV IgM antibodies were detected in 29.2 per cent of our

children with AES which may be considered a possible herpes infection as we could not detect any HSV PCR positivity in CSF which is confirmatory. This may be due to delayed presentation to tertiary care centres, late sample collection and processing, and prior antiviral therapy. JE is the predominant aetiology for AES in different parts of India. In this study, JE was positive in 27 (3.1%) children with AES. HSV encephalitis is one of the common viral aetiologies for AES which is reported in almost 11-14 per cent of children with AES in various studies across the globe. Almost 30 per cent of the children with HSV encephalitis had anti-NMDAR encephalitis as reported in a retrospective study by Pruss *et al*[22]. Previous epidemiological studies mostly focused on confirmatory cases of HSV, hence using PCR as a modality of investigation resulting in a lower rate of positivity. The current study not only focused on the confirmatory cases but also looked at exposure to HSV which is considered as one of the triggering factors for AIE in literature, mostly in retrospective studies. As we had screened for antibodies (both IgM and IgG) against HSV, our results showed a higher prevalence of positivity suggesting possible infection. This may be due to the endemicity of the virus attributed to the trigger. This finding further substantiates the proposed hypothesis of HSV-triggered AIE which may need further confirmation in future studies. Other than HSV, parvovirus, JE virus, HSV II, and HHV7 were also positive in our study sample which is similar to previous reports indicating association with anti-NMDAR encephalitis[23].

There was a significant delay in diagnosis of AIE from the onset of illness in this study as compared to viral aetiologies. This may be due to late suspicion or delayed presentation to tertiary care centres. Most of these children were managed initially as AES with possible viral or bacterial origin and referred when there was poor response to treatment or recurrence of symptoms. Armangue *et al*[24] reported the median interval between HSV encephalitis and AIE to be 26 (24-32) days which is similar to the findings in this study[24].

Children with anti-NMDAR encephalitis presented with seizure as one of the common clinical features which is observed in almost 80 per cent of the children in this study. Similar results were reported by Chowdhury *et al*[20] in the retrospective analysis of cases from India among the paediatric age group[20]. Apart from seizure and altered sensorium, movement disorders, and behavioural problems were the other features usually associated with AIE. In the current study, movement disorder was only observed in 27 per cent of children which is lower than what is reported in a previous study[20]. This may be due to early initiation of treatment in most cases with AIE. There was not much difference in clinical features of anti-NMDAR encephalitis and HSV encephalitis except for behavioural problems and movement disorder which were more common in earlier group[25]. There was not much difference in the CSF examination except for higher protein in HSV encephalitis. CSF pleocytosis with or without elevated protein has been reported in few cases of anti-NMDAR encephalitis but it has not been observed uniformly as in ours to contribute to diagnosis[26].

Though there are no standard recommendations for treatment for AIE, immunosuppressants remain the cornerstone of management including anti-NMDAR encephalitis. Steroids and IVIg are considered to be the first line of therapy. In our cohort almost 31 (84%) children received IVMP followed by oral steroid. A similar treatment protocol has been reported by Titulaer *et al*[27] where 87 per cent of the children had received steroids.

Following treatment, 32 (86.4%) of the children in this study were discharged from the hospital. Eleven (29.7%) had complete recovery at discharge while 21 (56.7%) had sequelae in the form of poor sensorium or abnormal movement. However, at six-month follow up, 22 (59.4%) children had complete recovery without recurrence whereas 10 (27%) had neurological sequelae (altered sensorium or behavioural abnormality). Chowdhury *et al*[20] reported similar outcomes in their retrospective analysis of paediatric cases where 56 per cent had improved whereas 40 per cent had sequelae. However, these are the retrospective data where the duration of follow up and recurrence were the limitation and have not been recorded. In a prospective cohort study by Titulaer *et al*[27], the treatment response was 53, 80 and 90 per cent at four, 12 and 24 months follow up, respectively. However, this study includes both children as well as adults. Separate treatment response rates have not been mentioned in the study. Complete recovery in children with possible HSV encephalitis was 64.6 per cent at discharge whereas neurological sequelae were there in 19.5 per cent of children. A meta-analysis of nine studies reported a prevalence of neurological sequelae up to 50.7 (39.2-62.2%) per cent. However, all these studies included children with confirmed HSV encephalitis by PCR evaluation only[28].

The major strength of the present study lies in the fact that it is a prospective study where children with anti-NMDAR encephalitis were evaluated for associated CNS viral infection which may trigger AIE. Children were followed up for six months to look for treatment outcomes and relapse. The limitation of the study is that late presentation of cases and investigation thereof would have resulted in missing some early warning signs if so to suspect AIE early as well as picking up viral detection in CSF by PCR assay.

Overall, anti-NMDAR encephalitis is one of the major causes of AES in children. Post-viral triggered autoimmune encephalitis is more common than what is reported and usually, these children respond to immunosuppressants if treated early. Though clinically it is difficult to differentiate from common mimickers like viral encephalitis, children presenting with behavioural problems and movement disorders should be evaluated for AIE. Early diagnosis and treatment with immunosuppressants result in better neurological outcomes. Children with viral encephalitis should be treated adequately and followed up regularly for early diagnosis of autoimmune encephalitis.

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