ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Feb 15; 6(2):423-429.
https://doi.org/10.3889/oamjms.2018.103
eISSN: 1857-9655
***Public Health***

# Epidemiological Profile of Acute Viral Encephalitis in a Sample of Egyptian Children

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**Citation:** Meligya B, Kadryb D, Draz IH, Marzouka H, El Baroudya NR, El Rifay AS. Epidemiological Profile of Acute Viral Encephalitis in a sample of Egyptian Children. Open Access Maced J Med Sci. 2018 Feb 15; 6(2):423-429. https://doi.org/10.3889/oamjms.2018.103

**Keywords:** Viral encephalitis; Pediatric; PCR; Outcome

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**Received:** 04-Jan-2018; **Revised:** 03-Feb-2018; **Accepted:** 09-Feb-2018; **Online first:** 14-Feb-2018



**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist

**Abstract**

**INTRODUCTION:** Acute encephalitis syndrome (AES) is a considerable public health problem.

**AIM:** This study was designed to describe the aetiology, demographic features, clinical picture, short-term outcome and risk factors of mortality of children with viral encephalitis in Egyptian children.

**METHODS:** PCR detection of viruses in the CSF of pediatric patients admitted to the pediatric unit or ICU Cairo University Pediatric hospital presenting with encephalitis syndrome.

**RESULTS:** Of the 96 patients included in the study, viral etiological agents were detected in 20 cases (20.8%), while 76 patients (79.2%) had no definite viral aetiology. The most abundant virus detected was Enterovirus (EV) in fourteen (14.5%), two (2.1%) were positive for human herpes simplex virus 6 (HSV-6), one (1.0%), human herpes simplex virus1 (HSV-1), one (1.0%) Epstein Barr virus (EBV), one (1.0%), cytomegalovirus (CMV) and one (1.0%) with varicella-zoster virus (VZV). On the short term outcome, 22 (22.9) patients died, and 74 (77.1%) survived. Severity outcome among survival was vegetative in three cases (4%) severe in 9 (12.16%), moderate in 14 (18.9%), mild in 29 (39.2%) and full recovery in 19 (25.6%). Mortality risk factors for younger age, the presence of apnea, the need for mechanical ventilation and the presence of abnormal CT findings were all significantly associated with fatal outcome ($p < 0.05$).

**CONCLUSION:** Enterovirus was the most common cause of encephalitis among Egyptian children. Mortality was correlated with younger age and disease severity at admission. Sequelae were high among infected children.

## Introduction

Encephalitis is a critical, potentially lethal condition that can cause a variety of viral, bacterial, parasitic, as well as from toxins and autoimmune reactions to vaccines [1].

Although viruses are considered as the most important etiological agents of encephalitis worldwide [2], viruses are often poorly understood the cause of encephalitis. In more than 60% of encephalitis, a demonstrable etiologic agent cannot be identified [3] [4] [5].

Acute viral encephalitis (VE) is an unusual presentation of viral infections which affects children and young adults mainly after viral invasion of the central nervous system presenting by 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 in a person of any age at any time of year [2] [6].

A range of neurotropic viruses is involved in acute viral encephalitis [7]. Moreover Every day new viruses are being associated with encephalitis of varying severity making specific diagnosis challenging [6].

Herpes Simplex virus (HSV) - 1 is the virus most commonly involved in sporadic fatal encephalitis; however, other viruses engaged in encephalitis include herpesviruses (HSV - 2, varicella-zoster, cytomegalovirus, Epstein - Barr, and HHV 6 and 7); paramyxoviruses (measles, rubella); orthomyxoviruses (influenza A virus); enteroviruses (EV 70 and 71, polio -, echo - and coxsackieviruses);

flaviviruses (West Nile, Japanese encephalitis, dengue and Zika viruses); retroviruses (human immunodeficiency virus); alphaviruses (Venezuelan equine -, eastern equine -, western equine - encephalitis); bunyaviruses (La Crosse virus); rhabdoviruses (rabies virus); parvovirus (B19); and astroviruses [8] [9] [10] [11] [12].

In the absence of pathologic evidence of brain inflammation, diagnosis of encephalitis can be inferred from an inflammatory response in the CSF or the presence of abnormal neuroimaging consistent with parenchymal affection and can be used as surrogate markers of brain inflammation [13].

The estimated incidence of encephalitis has a wide variability and is dependent upon age, demographics, climate, the presence of natural host for causative agent, and presence of epidemic illness [14].

Identifying the aetiology of encephalitis is challenging. The definition varies, and distinguishing encephalitis from meningoencephalitis or even meningitis or encephalopathy can be difficult [15].

Improving the diagnostic tools for encephalitis using PCR rather than tissue cultures has increased the yield of etiologies [16] [17].

Most studies performed to detect viral causes of childhood encephalitis are done in western or Asian countries, while the literature has a paucity of data in the Middle Eastern region [1] [9] [12].

This study was done to acknowledge the etiological viral causes of childhood encephalitis in Egypt and to demonstrate the clinical features, seasonal variations and short-term outcome of the cases.

## Methodology

This two - year prospective cohort study conducted on children diagnosed with encephalopathy syndrome selected from those admitted to the pediatric unit or pediatric ICU Cairo University Pediatric hospital during a search period all over the whole year.

### *Ethical consideration*

The study was designed to conform to the requirements of the latest revision of Helsinki Declaration of Bioethics [18]. The researcher obtained the approval of the medical ethical committee of the National Research Centre and the ethical committee of Research Committee of Pediatrics Department-Faculty of Medicine - Cairo University. Signed informed consents were collected from the legal guardian of the children before enrolment and after explanation of the aim and nature of the study.

### *Inclusion criteria*

All pediatric patients from the age of 1 month to 13 years presented by encephalopathy syndrome were included in the study.

Acute encephalopathy was defined using The Consensus Statement of the International Encephalitis Consortium; Encephalitis was defined as acute encephalopathy fever with alteration of consciousness and/or with neurological deficit, secondary to central nervous system involvement lasting more than 24 hours, and not more than a one-week history [13].

### *Exclusion criteria*

Other causes of encephalopathy as a brain tumour, vascular disorders, intoxication, or psychosis, traumatic brain injury, pre-existing neurological conditions as metabolic encephalopathy or epilepsy, febrile seizure.

Bacterial meningitis was excluded by the clinical picture of the patient with severe irritability and signs of meningeal irritation with positive CSF bacterial cultures, other infectious etiologies as brain abscess, acute organ dysfunction detected from clinical examination and lab finding.

### *Data collection*

Demographic data as age, sex and season were included. Clinical data as full history and neurological manifestations were recorded. The place of admission whether hospital ward or intensive care settings or the need for mechanical ventilation was mentioned.

In addition to the routine lab investigations, CSF cell count, chemistry and culture were also done. Pleocytosis was defined with CSF cells >15 cells/$mm^3$ for infants aged 1 to 2 months, and >5 cells/mm3 for patients aged >2 months; lymphocytes predominance if > 60%, high CSF proteins if > 45 mg/dL, CSF glucose: serum ratio should be 60%.

Urgent non - contrast CT imaging of the brain was done whenever indicated, not all patients were followed by MRI due to the extreme difficulty in transferring patients to the radiology unit especially if clinically unstable or if the patient was on mechanical ventilation. However resonant magnetic imaging (MRI) was scheduled upon discharge to the ward.

Patients were managed symptomatically until a definite cause could be found. All patients received acyclovir on admission and continued for 14-21 days when diagnosed with herpes virus or stopped if diagnosed otherwise, and received the appropriate

treatment; discussing treatment is beyond the scope of our research.

The clinical course of the patient is followed for a short term during his hospital stay, and case lethality was recorded whether he survived or discharged.

The neurological outcome of the survived patients was classified according to pediatric cerebral overall category scale into, no squeal, mild, moderate, severe, vegetative and brain dead [19].

### *Laboratory investigations*

Nucleic acid extraction, reverse transcription and PCR amplification

RNA extraction was done automatically using QIAamp MinElute Virus Spin Kit (QIAGEN) Cat. No (57704), on QIA cube machine. cDNA was synthesised by reverse transcription using RevertAidTM First Strand cDNA Synthesis kit Cat.No. (K1622 SG1300)(Fermentas, Ontario, Canada), accords to manufacturer's instruction. cDNA was stored at -80°C until processed.

In PCR, efficiency can be reduced by inhibitors that may be present in the clinical specimen An Internal Control (Meningitis ACE IC) is supplied. This allows the user both to control the nucleic acid isolation procedure and to check for possible PCR inhibition. The Internal Control is introduced into each specimen before nucleic acid extraction and is co-amplified with target nucleic acid from the clinical specimen. Also; the 8 - methoxypsoralen (8 -MOP) system is used to extinguish the template activity of contaminated DNAs. 8 - MOP is known to intercalate into double-stranded nucleic acids and form a covalent interstrand crosslink after photoactivation with incident light of a wavelength of 320 - 400 nm. The Seeplex Meningitis - V2, employs a "Dual Priming Oligonucleotide (DPOTM) technology, which provides freedom in primer design and PCR optimisation and maximises PCR specificity and sensitivity. Briefly, PCR amplification was performed using 5 µL of cDNA, 2 µL of 10X MV2 primer mixture, 3 µL of 8 - MOP and 10 µL of 2X Multiplex Master Mix (Seegene Inc.) in a total volume of 20 µL. The 2X Multiplex Master Mix contains dNTP and enzyme for the specific amplification of the pathogen's genome and 10X ACE PM is the primer mixture for the specific target amplification. The amplification protocol was as follows: initial denaturation at 94°C for 15 min, 40 cycles of denaturation at 94°C for 30 sec, annealing at 63°C for 90 sec, extension at 72°C for 90 sec, and final annealing at 72°C for 10 minutes. The amplified PCR products were electrophoresed in 2% agarose gels and stained with ethidium bromide.

### *Statistical method*

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data were summarised using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the non-parametric Mann-Whitney test [20]. For comparing categorical data, Chi-square ($\chi 2$) test was performed. The exact test was used instead when the expected frequency is less than 5 [21]. P - value less than 0.05 was considered as statistically significant.

## Results

The study was conducted from first January 2015 to 31th of December 2016. One hundred twenty children admitted with criteria encephalopathy syndrome were enrolled in the study in either general pediatric units or intensive care units. Twenty four patients were excluded from investigation (as revealed other reasons for presentation, e.g. systemic lupus encephalitis, acute disseminated encephalomyelitis, brain abscess, or vasculopathy.

Ninety-six patients were eligible for the study, 60 (62.55%) were males, and 36 (37.5%) were females, 50 (52%) needed intensive care admission, while 43 (44.8%) needed mechanical ventilation.

**Table 1: Demographic and clinical finding of studied cases**

| | | | |
|---|---|---|---|
| Age (months) | | | |
| | Mean ± SD | 29.34 ± 28.29 | |
| | Range | 1-120 | |
| The length of hospital stays (days) | | | |
| | Mean ± SD | 15.42 ± 15.53 | |
| | Range | 2 -107 | |
| | | Frequency | Percent |
| Gender | | | |
| | Female | 36 | 37.5% |
| | Male | 60 | 62.55% |
| Seasonal variation | | | |
| | Summer | 37 | 38.5% |
| | winter | 30 | 31.2% |
| | Spring | 16 | 16.7% |
| | Autumn | 13 | 13.5% |
| Clinical data | | | |
| Coma | | 77 | (80%) |
| Fever | | 68 | (70%) |
| Seizures | | 64 | (66%) |
| increased intracranial pressure | | 14 | (14%) |
| irritability | | 13 | (13%) |
| focal deficits | | 7 | (7%) |
| Intensive care admission | | 50 | 52% |
| Mechanical ventilation need | | 43 | 44.8% |
| CT imaging finding | | | |
| Normal | | 67 | 69.8% |
| Brain Edema | | 23 | 24.0% |
| Hypodense areas of hypoxia. | | 6 | 6.25% |
| Severity outcome among survival* | | | |
| vegetative | | 3 | 4% |
| severe | | 9 | 12.1% |
| moderate | | 14 | 18.9% |
| mild | | 29 | 39.2% |
| Full recovery | | 19 | 25.6% |
| Mortality rates n | | | |
| Death | | 22 | 22.9 |
| Survived | | 74 | 77.1 |

The age of patients ranged from 1 month-12 years (mean 29.34 + 28.29). The majority of patients presented during summer (37 or 38.5%), and winter (30 or 31.2%), while minority presented during spring (16 or 16.7%) and autumn (13 or 13.5%).

Clinical manifestations of the studied patients included: coma or disturbed conscious level in 77 (80%) patients, fever in 68 (70%) patients, seizures in 64 (66%) patients, increased intracranial pressure 14 (14%) patients, irritability in 13 (13%) patients and focal deficits in 7 (7%) patients.

The length of hospital stay was 2 -107 days (15.42 ± 15.53). CT imaging finding was normal in 67 (69.8%) of cases, while twenty -three (24.0%) revealed brain oedema. Six cases (6.25%) showed hypodense areas of hypoxia. On the short - term outcome 22 (22.9%) patients died, and 74 (77.1%) survived (Table 1).

CSF pleocytosis ranged from 0 - 300 (46 ± 59), lymphocytes predominated in 76 (79.2%), and polymorphnuclear cells in 19 (19.8%), CSF was acellular in one case that was neutropenic and acquired CMV infection. CSF glucose level ranged from 10 - 127 mg/dL (62.12 ± 24.06) and CFS proteins 5 - 305 gm/dL (47.7 ± 46.43)

Viral etiological agents were detected in 20 cases (20.8%), while 76 patients (79.2%) had no definite viral etiology. The most abundant virus detected was EV in fourteen (14.5%), two (2.1%) were positive for HSV - 6, one (1.0%) HSV - 1, one (1.0%) EBV, one (1.0 %)CMV and one (1.0%) with VZV (Table 2).

**Table 2: Laboratory and CSF finding of studied cases**

| CSF finding | Frequency | Percent |
|---|---|---|
| Lymphocytes predominance | 76 | 79.2% |
| Polymorphonuclear cells predominance | 19 | 12.1% |
| Acellular | 1 | 1% |
| CSF glucose level mg/dl | | |
| | Mean ± SD | 62.12 ± 24.06 |
| | Range | 10-127 |
| CFS proteins level gm/dl | | |
| | Mean ± SD | 47.7 ± 46.43 |
| | Range | 5-305 |
| Viral etiological agents | Frequency | Percent |
| Ev | 14 | 14.5% |
| Hsv - 6 | 2 | 2.1% |
| Hsv - 1 | 1 | 1% |
| EBV | 1 | 1% |
| Cmv | 1 | 1% |
| Vzv | 1 | 1% |
| No virus detected | 76 | 79.2% |

Severity outcome among survival according to pediatric cerebral performance category scale were vegetative in three cases (4%) severe in 9 (12.16%), moderate in 14 (18.9%), mild in 29 (39.2%) and full recovery in 19 (25.6%).

Table 3 demonstrate clinical picture according to the causative virus; there was no significant difference between clinical presentation, CSF finding or outcome.

**Table 3: Demographic, clinical of studied cases according to the causative virus**

| | EV (*n* = 14) | HSV-1 (*n* =1) | HSV-6 (*n* = 2) | EBV (*n* =1) | CMV (*n* =1) | VZV (*n* =1) | No virus (*n* = 76) |
|---|---|---|---|---|---|---|---|
| Demographic data | | | | | | | |
| Age (median in months) | 19 | 24 | 24 | 14 | 67 | 48 | 18 |
| Sex, (n, percentage) | | | | | | | |
| male | 10 (10.4%) | 1(1%) | 2 (2%) | 1 (1%) | | | 46 (48%) |
| female | 4 (4.1%) | | | | 1 (1%) | 1(1%) | 30 (31%) |
| Season | | | | | | | |
| Summer | 4 (4.1%) | 1(1%) | | | | | |
| Winter | 3 (3.1%) | | 2 (2%) | | | | |
| Spring | 4 (4.1%) | | | | | | |
| Autumn | 3 (3.1%) | | | 1(1%) | 1(1%) | 1(1%) | |
| Clinical data | | | | | | | |
| Coma n (percentage) | 12 (12.5%) | 1(1%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) | 62 (64.5%) |
| Irritability n (percentage) | 1 (1%) | 0 | 1 (1%) | 1 (1%) | 0 | 0 | 10(10.4%) |
| Increased ICP n (percentage) | 2 (2%) | 0 | 0 | 0 | 0 | 0 | 12 (12.5%) |
| Motor n (percentage) | 2 (2%) | 0 | 0 | 0 | 0 | 0 | 6 (6.25%) |
| MV | 5 (5.2) | 0 | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) | 32 (33.3%) |
| Mortality n (percentage) | 5 (5.2%) | 0 | 0 | 0 | 1 | 0 | 16 (16.6%) |
| Neurological deficits | 3 (3.1%) | | | | | | 16 (16.6%) |
| 0 | 2 (2%) | 1 (1%) | | 1 (1%) | | | 24 (14.58) |
| Mild | 2 (2%) | | 1 (1%) | | | | 11 (11.45%) |
| Moderate | 1 (1%) | | | | | 1 (1%) | 8 (8.3%) |
| Severe | 1 (1%) | | 1 (1%) | | | | 1 (1%) |
| vegetative | | | | | | | |

EV: enterovirus; HSV: herpes simplex virus, EBVEpstein Barr virus, CMV cytomegalovirus; VZV: varicella zoster virus; CSF: cerebrospinal fluid, ICPintracranial pressure, MV: mechanical ventilation.

Mortality risk factors assessment demonstrated that the younger age, the presence of apnea, the need for mechanical ventilation and the presence of abnormal CT finding as brain oedema and hypodense areas were all significantly associated with fatal outcome ($p < 0.05$) Table 4.

Five cases among EV group died making mortality within the group 35.7%. Another CMV case died, this case was brain dead on admission.

**Table 4: Risk Factors for mortality**

| | *the* |
|---|---|
| Age | 0.027* |
| Sex | 0.380 |
| Pleocytosis | 0.099 |
| Coma | 0.108 |
| Fever | 0.762 |
| Seizures | 0.647 |
| Apnea | 0.001 |
| Motor deficit | 1 |
| Mechanical ventilation | < 0.001* |
| Edema of CT | 0.004* |
| Virus Type | 0.392 |

* ($p < 0.05$) is considered significant

## Discussion

Viral encephalitis is a significant cause of childhood morbidity and mortality. Up to 60% of cases of suspected viral encephalitis remain unexplained due to the failure of routine laboratory techniques to detect an infectious agent [22].

In our study, the incidence of confirmed cases of viral encephalitis was 20.6%. Although this percentage is lower than our studies to some extent [15] [23], but it is similar to many other studies [12]

[13] [24] Moreover with studies with large time scale and larger sample size as the prospective study held by California Encephalitis Project (CEP) all over 7 years and included 1570 cases of encephalitis which revealed only 16% of encephalitis cases had a confirmed or probable etiology [25].

Accurate diagnosis and immediate management of viral encephalitis are critical to reducing complications and fatality rates [26] A diagnostic gap is still present although the progress that had taken place with both traditional and molecular biological technologies in detecting the causes of viral encephalitis.

The current study aimed to acknowledge the etiological viral causes of childhood encephalitis in Egypt and to demonstrate the clinical features, seasonal variations and short-term outcome of the cases.

Many studies set in Western industrialised countries tend to focus on HSV, VZV, EBV, EV, respiratory viruses or bacterial encephalitis [25] [27]. In contrast, Asian countries are faced with a high incidence of arboviruses as Dengue virus and Japanese encephalitis virus [28] [29] [30].

As few data was found on viral encephalitis in developing countries and there was no clear published data on viral encephalitis in Egyptian children. Fourteen cases were caused by EV infections; which was the most abundant virus in the study; there was no specific temporal relation to any season of the year.

Two (2.1%) were positive for HSV - 6, one (1.0%) HSV - 1, one (1.0%) EBV, one (1.0%) CMV and one (1.0%) with VZV. This change of encephalitic viral epidemiology is related to the widespread of vaccination, making HSV-1 dethroned as the most common cause of viral encephalitis among children. Incidence of EV ranged from less than one, to 25% in previous studies [25] [28] [31] [32] [33].

The study addressed the clinical profile and short-term complication of the viral encephalitis. There was male preponderance in our study (62.55%); this was in keeping with most studies [32] [34]. Reasons for higher male incidence could be due to more exposure to the causative agents or the underlying genetic makeup of a male. Clinical manifestations among different etiologies were mostly imperceptible, except for rabies patient who developed laryngospasm and hydrophobia after exposure to a dog bite. As previously mentioned in other studies, in the current study coma was the most common presentation [35] [36].

CSF pleocytosis is suggestive of an inflammatory process of the brain, the lack of CSF pleocytosis, however, does not exclude encephalitis. It is recognised that the CSF may be devoid of cells in immunocompromised patients [37] or early during infection [38].

Forty-five percent to 55% of children with viral encephalitis will show a CSF lymphocytic pleocytosis, although within the first 48 hours this may be neutrophil-predominant [39].

Case fatality in our study was 22.9%, and this was significantly associated with younger age, the presence of apnea, the need for mechanical ventilation and was highly significant with the presence of abnormal CT finding. All of these risk factors indicate disease severity.

In general the overall case fatality of viral encephalitis is between 0% and 29% [27] [32] [40] [41].

Mechanical ventilation was a risk factor of fatality in Mailles and his colleagues in France, 2007 [23]. While younger age and low Glasgow Coma Score (GCS) were risk factors [28]. Immunocompromise was a major mortality factor in the study population in England [42]. Patients with normal neuroimaging studies were more likely to recover than patients with abnormal neuroimaging ($P = 0.008$.) The risk of death or severe damage in patients less than 1 year of age was 5.0 - fold ($p < 0.001$) greater than that of older children [43]. Among survivals, there were neurological sequelae in 74.32%, in the present study. That was higher than other studies which reported sequelae in 25 – 69% [35] [36].

The limitations of our study were a high proportion of unknown causes, which may be due to a later presentation of cases beyond the detection timeframe of PCR, the elimination of other extra - CSF sites for molecular sampling, the presence of a viral cause that is deficient in our labs diagnostic assays, the presence of non - infectious cause of encephalitis as autoimmune encephalitis, or the presence of a new virus. Owing to the high prevalence of EV in the study group, it is recommended to include PCR for EV in the routine workup of encephalitis.

In summary, enterovirus was the most common cause of encephalitis among Egyptian children. There was a high percentage of unknown cases. Mortality was correlated with younger age and disease severity at admission. Sequelae were high among infected children.

## Acknowledgement

The authors would like to thank Dr May Sherif, clinical pathologist for her aid in interpreting PCR results.

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