Original Article

Ophthalmology and Allied Sciences
Volume 3 Number 1, January - June 2017
DOI: http://dx.doi.org/10.21088/oas.2454.7816.3117.4

Ocular Findings in Encephalitis Patients: A Clinical Study

Ramyash Singh Yadav*, Aprajita Chaudhary,Deepti Yadav***, Komal Prasad Kushwaha****, Sunil Gupta*****

*Associate Professor, ***Resident, Department of Ophthalmology, ****Professor, Department of Paediatrics, B.R.D. Medical College, Gorakhpur. **Associate Professor, Department of Ophthalmology, M.L.N. Medical College, Allahabad. *****Consultant, Shau Rameshwaran Kothiwal Hospital, Kath Road, Moradabad.

Abstract

Objective: To observe incidence, recovery rate and extent of recovery in ocular manifestation of viral encephalitis. *Method:* All the patient with symptoms of encephalitis in the age group of 6 months to 14 years; Attending the Paediatric OPD with admission and eye OPD of B.R.D. Medical College will be included in this study. The details in infant include weight, age of presentation, gender significant neonatal problem and ocular findings up to a period of 6 months. All the children underwent a detailed paediatric examination by a paediatrician. *Result:* The findings of the study are based on 118 patients of Acute Encephalitis Syndrome. Maximum number of children were 6-10 year of age group , 47 children which covers 38.97 % cases. 58.47 %(69 children) of total cases being male and 41.53 %(49 children) of cases being female .In our study number of children showing any ocular finding were 44 i.e. 37.29% of total cases and the remaining 74 children i.e. 62.71 % cases does not show any ocular finding. Ocular findings include conjunctivitis, seen in 18 children, Subconjunctival hemorrhage in 6 children , corneal ulcer in 4 children, exposure keratitis in 16 children, iritis / Iridocyclitis seen in 3 children , Papilloedma in 12 children and CN Palsy in 2 children .Patients of conjunctivitis , Subconjunctival hemorrhage , exposure keratitis and iritis / Iridocyclitis recover completely without leaving any ocular deformity. Corneal ulcer is seen in 4 patients. These are all unconscious patient having GCS < 9 and malnutrition grade III &IV. These patients treated conservatively and in a follow up period of 1 month all patient recovered leaving nebular/*macular grade corneal opacity* in 2 patients. At time of admission 12 children had Papilloedma. In a follow up period of 6 months it resolved in 10 children without leaving any ocular deformity but in 2 children Papilloedma resolved with leaving post oedema optic atrophy. 2 children had 6th Cranial Nerve palsy without recovery in a follow up period of 6 month. Ocular manifestation of Vitamin A deficiency is seen in 13 children (6 male, 7 female). So total of 8.7 % male population of AES show vitamin A deficiency while 14.29 % of female population show the deficiency. Children showing untreatable blindness in our study were 18 (10 male, 8 female). Causes of untreatable blindness are post oedema optic atrophy in 2 children (1 male, 1 female) and retro bulbar neuritis / higher cortical lesion in 16 children (9 male , 7 female). 4pts of treated population suffer visual disability. *Conclusion*: Various observations in our study have clearly indicated that AES is more common in young males in rural area. Children showing ocular finding were 44 i.e. 37.29% of total population and the remaining 74 children i.e. 62.71% population does not show any ocular finding. Ocular manifestation of Vitamin A deficiency is seen in 13 children (6 male , 7 female). Children showing untreatable blindness in our study were 18 (10 male, 8 female). Causes of untreatable blindness are post oedema optic atrophy in 2 children (1 male, 1 female) and retro bulbar neuritis / higher cortical lesion in 16 children (9 male, 7 female). So 15.25 % treated population suffer visual disability. 2 children show 6th Cranial Nerve palsy without recovery in a follow up period of 6 month. 2 children show nebular /macular grade corneal opacity. So ocular damage and blindness is quiet common in AES. All children should undergo a thorough ophthalmological examination and follow up.

Keywords: Acute Encephalitis Syndrome (AES); Blindness; Optic Atrophy; Eastern UP.

Reprint Request: Ramyash Singh Yadav, Type-4/32, B.R.D. Medical College, Gorakhpur, Uttar Pradesh 273013.

E mail-ramyashyadav93@yahoo.in

Recived on 13.12.2016, **Accepted on** 04.01.2017

Introduction

Encephalitis is a serious devastating illness prevalent in eastern region of Uttar Pradesh, for so many years, causing both morbidity and mortality.

The cases of encephalitis are now prevalent throughout the year but there is sudden increase in number of Japanese Encephalitis and Non-Japanese Encephalitis (JE) in the month of August to November [1]. About 20% children are immunologically incompetent and have behavioural problems [7]. Virus Encephalitis is caused by different viruses, or by different serotypes of some virus [2,3]. It occurs as a sporadic disorder or in form of sudden outbreaks. In India JE virus causes major epidemics and endemic in many regions including Gorakhpur region of Eastern U.P [4,5]. As part of the effort to control Japanese encephalitis (JE), the World Health Organization (WHO) is producing a set of standards for JE surveillance [4]. The surveillance consists of identifying patients with acute encephalitis syndrome (AES), and then classifying the patients according to the results of laboratory diagnostic tests. AES is defined as the 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 seizures) in a person of any age at any time of year [4,5].

In AES there is increase in intracranial pressure which can be consequent to an increased production of fluid or to a decrease in out flow facility [6].

A large no patient of AES are unconscious at the time of admission, many of these patient have a swollen lid due to a generalized inflammatory body reaction. Such patient suffers from exposure keratitis, conjunctivitis, iritis, Iridocyclitis, choroiditis, vitritis and corneal infection. Such patient of long duration also suffer corneal ulceration, these ulcer when heal leave a corneal opacity. Most patient of raised ICT seeks treatment of headache. The patient may complain of decrease visual acuity , transient obscuration of vision , enlarged blind spot or diplopia (due to 6^{th} nerve palsy) [8]. 6^{th} CN Palsy is a nonspecific sign of Papilloedema. The principal pathophysiology of optic disc oedema in AES may be the axoplasmic stasis, oedema or vascular congestion due to generalized body viremia [9]. AES caused by some viruses especially by CMV and AIDS virus can lead to chorioretinitis and acute retinal necrosis [10]. But this is a very rare finding. In patient of AES chronic Papilloedma may lead to injury of optic nerve and secondary optic atrophy with permanent loss of vision.

Enteroviruses are also associated with major central nervous system infection with diverse clinical syndrome such as a minor febrile illness, to severe potential fatal illness viz [11]. aseptic meningitis, meningoencephalitis, acute flaccid paralysis, myocarditis and neonatal entero viral multi organ failure [12-15]. AES child which get recovery from disease suffer from major and minor neurological deficit . Such deficits usually occur in association with behavioural problem [16]. Neurological deficit in children include impaired memory, extra pyramidal sign, speech deficit, convulsion, involuntary movement, mental retardation, hemi paresis, CN Palsy and cerebellar sign [17,18].

So far more than 80 serotypes have different temporal pattern of circulation and are associated with different clinical manifestations [19]. Outbreaks of enterovirus, mediated encephalitis have been mainly described with EV-71 in Taiwan and other countries in Southeast Asia region [20,21]. Other human enterovirus have been associated with meningitis and acute flaccid paralysis (AFP) including recently described novel serotype of EV-76, 89, 90, 91 and Coxsackie virus [5,8,22,23].

In encephalitis the ocular symptoms ranges from mild irritation to vision threatening blindness depending upon the part affected and extent of damage [24,25].

Materials and Methods

All the patient with symptoms of encephalitis in the age group of 6 months to 14 years; attending the Paediatric OPD with admission and eye OPD of B.R.D. Medical College from June 2007 to September 2008 were included in this study. The detail in children include weight, age of presentation, gender significant neonatal problem and ocular findings up to a period of 6 months. All the children underwent a detailed paediatric examination by a paediatrician. Symptoms of viral encephalitis, distinctive features associated with a typical Japanese Encephalitis (JE) case like high grade fever associated with headache and vomiting, hypertonia, exaggerated Deep Tendon Reflex(DTR), extensor plantar have been seen.

Cases with encephalitis not showing typical JE features are grouped into "Non-JE". Cases with features of viral encephalitis & showing distinctive features like moderate grade fever, hypotonia, diminished DTR, inelicitable planters and any one of features like puffiness of the face, oedema feet, tachypnea, signs of congestive cardiac failure,

spleenomegaly and hepatomegaly etc. are grouped into Non-JE.

Grading of Severity

Classification of nutritional status using WHO/ CDC growth chart, Classification of ocular manifestation of vitamin-A deficiency using WHO xerophthalmia classification, Level of consciousness using modified GCS score.

Diagnostic Criteria

Febrile children with change in level of consciousness, with or without seizure or convulsion, CSF finding ***(Nelson Paediatrics, 18th ed.)***-Normal blood sugar, Pleocytosis, Slightly raised protein, Sterile CSF for bacteria culture.

Exclusion Criteria

Children conscious less than 1 hour,<6 months of age, Children with turbid CSF, Purpuric rashes, Ventriculomegaly found on CT scan, CSF finding suggestive of bacterial or tubercular meningitis.

Ophthalmic Examination

The initial examination of eye should assess symmetry, conformation and gross lesions, the eye should be viewed from 2-3 fit away in good light, and with minimal restraint of head. The anterior ocular segment and pupillary light reflex are examined in detail with a strong light and decrease magnification in a darkened room. Baseline tests like the Schirmer tear test, fluorescein staining and tonometry may be followed by averting the eyelids for examination, and flushing the nasolacrimal duct and see external part of the eye, including the anterior segment. Disease of vitreous and fundus are evaluated by direct and indirect ophthalmoscopy (usually performed after mydriasis) and vision testing (if possible). Schirmer test is performed before topical anaesthesia is instilled. Fluroscein staining and eversion of the eyelids need not require topical anaesthesia.

Material

Snellens Chart, Slit lamp, Direct, indirect ophthalmoscopy, Fluorscein strip and Schirmer strip, Dilator (Atropine, Tropicamide), Schizot Tonometer.

Follow up

I) 48 hours of hospitalization, II) 7 days of hospitalization, III) 1 week post discharge, IV) 1month post discharge, V) 3months post discharge, VI) 6 months post discharge.

Results

Study started with 161 patients (82 male ,79 female). Among 161 patients only 118 patients fulfilled the criteria of continuous follow up period of 6 months. 43 patients dropped out during the study and hence excluded.

Table 1: Age wise distribution

Age group (in year)	No. of patients	Percentage (%)
½-2	8	6.78
3-4	11	9.32
4-5	11	9.32
5-6	12	10.17
6-7	13	11.02
7-8	11	9.32
9-10	9	7.63
10-11	13	11.02
11-12	10	8.47
12-13	9	7.63
13-14	11	9.32

Table 2: Residental distribution

Residential Area	No. of Patients	Percentage (%)
Rural	71	60.17 %
Urban	47	39.83 %
Total	118	

Table 3: Classification of nutritional status using WHO Growth Standard

z- scores	Male	Female	Total
1 - +1	31	21	52
1 - 2	36	24	60
< 2	16	12	28
> +2	5	5	10
+ 1- +2	16	14	30
Total	69	49	118

Table 4: Level of consciousness in children at the time of admission by Modified Glasgow Comma Scale

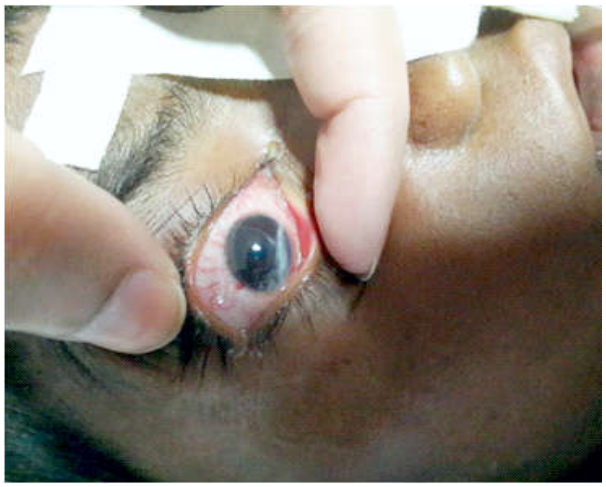
GCS Score	Male	Female	Total	Percentage (%)
15(normal)	21	13	34	28.81
14-12	18	16	34	28.81
12-9	11	7	18	15.25
9-7	13	8	21	17.80
<7	6	3	9	7.63

Table 5: Classification of ocular manifestation of Vitamin A deficiency using Xero-ophthalmia classification

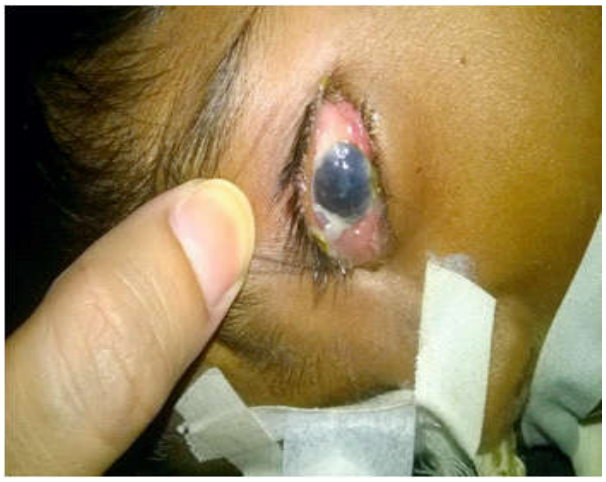
Grade	Male	Female	Total
XN	3	3	6
X1A	1	1	2
X1B	1	2	3
X2	0	1	1
X3A	1	0	1
X3B	0	0	0
XS	0	0	0
XF	0	0	0
Total	6	7	13

Table 6: Distribution of Ocular Findings at time of admission

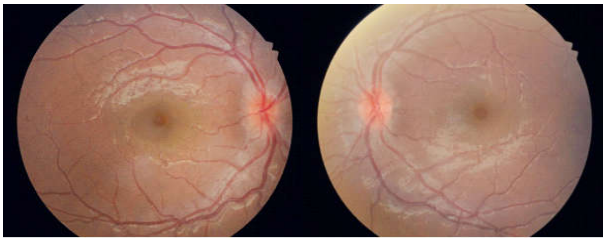
Ocular Manifestation	Male	Female	Total	Percentage (%)
Conjunctivitis	12	6	18	15.25
Subconjunctival hemorrhage	4	2	6	5.68
Corneal ulcer	3	1	4	3.39
Exposure keratitis	11	5	16	13.56
Iritis/Iridocyclitis	2	1	3	2.54
Papilloedma	8	4	12	10.17
Cranial nerve palsy	1	1	2	1.69
Total	41	20	61	51.69



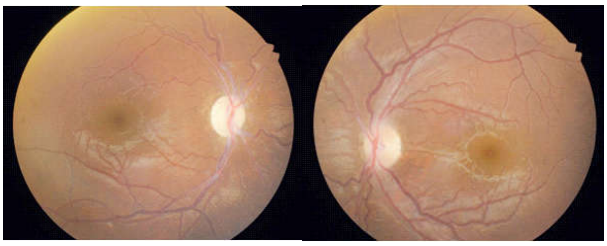
Picture 1: Exposure keratitis



Picture 2: Conjunctivitis



Picture 3: Early papilloedema



Picture 4: Optic atrophy

Table 7: Follow up of conjunctivitis in Hospitalized/ Discharge patient

Follow up in days	Male	Female	Total
2	12	6	18
7	4	2	6
14	0	0	0

All the patient of conjunctivitis recovered without leaving any ocular deformity.

Table 8: Follow up of Subconjunctival Hemorrhage in Hospitalized/ Discharge patient

Follow up	Male	Female	Total
2nd day	4	2	6
1 week	4	2	6
1 month	2	1	3
3 month	0	0	0

Table 9: Follow up of corneal ulcer in Hospitalized/ Discharge patient

Follow up	Male	Female	Total
2nd Day	3	1	4
1 week	2	1	3
1 month	1	0	1
3 month	0	0	0

All patient of corneal ulcer are treated conservatively. All the patient heal completely with leaving ***nebular / macular grade corneal opacity*** in 2 patients.

Table 10: Follow up of exposure keratitis in Hospitalized/ Discharge patients

Follow up	Male	Female	Total
2nd day	11	5	16
1 week	4	2	6
2 week	0	0	0

All patient of exposure keratitis are treated with proper cleaning, antibiotics, cycloplegic and lubricating eye drops. Unconscious patients are treated with pad and bandage .All the patients recover completely without leaving any ocular deformity.

Table 11: Follow up of iritis/iridocyclitis in Hospitalized/Discharge patient

Follow up	Male	Female	Total
2nd Day	2	1	3
1 week	1	1	2
2 week	0	0	0

All patients of iritis / Iridocyclitis treated conservatively without leaving any ocular deformity.

Table 12: Follow up of Ocular palsies (6th CN Palsy) in Hospitalized/ Discharge patient

Follow up	Male	Female	Total
2nd day	1	1	2
1 week	1	1	2
1 month	1	1	2
3 month	1	1	2
6 month	1	1	2

2 children show 6th cranial nerve palsy at admission which does not recover during a follow up period of 6th month.

Table 13: Papilloedma in Hospitalized patient at follow up

Follow up in Days	Male	Female	Total
2	8	4	12
7	8	3	11

Table 14: Follow up of discharge patient for Papilloedma

Follow Up	Male	Female	Total
1 week	8	3	11
1 Month	6	2	8
3 Month	1	1	2
6 Month	1	1	2

Table 15: Identification of untreatable cause of blindness in AES patients

	Retro bulbar Neuritis/ Higher cortical lesion	Post oedema optic atrophy
Male	9	1
Female	7	1
Total	16	2

Table 16: Blindness according to age and sex

Sex	½-5 year	6-10 year	11-14year	Total
Male	3	4	3	10
Female	2	4	2	8
	5	8	5	18

Table 17: Neurological Manifestation in AES

	No. of Patients	Percentage
Complete Recovery	76	64.41%
Behavioural Problem with no neurological deficit	3	2.54%
Minor Neurological Deficit	10	8.47%
Minor Neurological Deficit with behavioural problem	6	5.08%
Major Neurological Deficit	13	11.02%
Major neurological Deficit with behavioural problem	10	8.47%

Discussion

This is the *first study of this kind*, ocular findings in AES has not been reported *elsewhere.* The maximum no of children i.e. 47 were from 6-10 year age group forming 38.97% of population. 58.47% of total population being male and 41.53 % of population being female. 71 patient (60.17%) of total population belong to rural population while 47 patient (39.83%) were of urban population. Children are classified for nutritional status using WHO Growth Standard (W/A) classification. Among all children 70 children have normal range z-score i.e. 59.32%. 28 children were under nutrition (< 6 2 z-score) i.e. 23.73% and the 10 children were overweight (> + 2 z-score). At the time of admission 34children i.e. 28.8% population were of normal conscious level i.e. Glasgow Comma Score 15. So among all children 84 (71.19%) children found subnormal GCS Score. 34children (18 male, 16 female) were GCS Score 14-12, 18 children (11male, 7 female) were GCS Score 12-9 , 21 children (13 male, 8 female) were GCS Score 9-7 and the remaining 9 children (6male, 3 female) were of GCS Score <7 . In our study number of children showing any ocular finding were 44 i.e. 37.29% of total population and the remaining 74 children i.e. 62.71% population does not show any ocular finding. Ocular findings include conjunctivitis, seen in 18 children (12 male, 6 female) i.e. 15.25%, Sub conjunctival haemorrhages in 6 children (4 male, 2 female) about 5.68 % , corneal ulcer in 4 children (3 male 1 female) i.e. 3.39%, exposure keratitis in 16 children (11 male, 5 female) i.e. 13.56% , iritis/ Iridocyclitis seen in 3 children (2 male 1 female) i.e. 2.54%, Papilloedma in 12 children (8 male, 4 female)

i.e. 10.16% , and CN Palsy in 2 children (1 male 1 female) (Table 7).

All patient of conjunctivitis show watery discharge, boggy swelling of conjunctiva with minimal congestion. All 18 patients treated conservatively with antibiotic drops and proper cleaning of eye. 12 patient recover in a week period and the rest 6 patient recover in another week. Subconjunctival hemorrhage is seen in 6 patient, it is seen in all those patient having Papilloedma. The cause of Subconjunctival hemorrhage may be raised ICT due to which the pressure in subconjunctival vessels also rises and they rupture due to increase tension. In three month follow up period hemorrhage resolve in all patient without leaving any ocular deformity (Table 9). Corneal ulcer is seen in 4 patients. The cause of corneal ulcer is super infection on exposure keratitis and vitamin A deficiency. These are all unconscious patient having GCS < 9 and malnutrition grade III & IV. All these patient treated conservatively in a follow up period of 1 month all patient recover with leaving *nebular / macular grade corneal opacity* in 2 patients.16 patients show exposure keratitis. These are all unconscious patient having GCS <12. The reason behind exposure keratitis is incomplete closure of eyes because of unconsciousness and lid oedema. 6 of these patient also show lid swelling at time of admission .Lid swelling in these patients are the result of generalised body inflammation. All these patient treated conservatively and in a period of 2 week they recover completely without leaving any ocular deformity. Iritis / Iridocyclitis is seen in total 3 patient at time of admission , all these patient treated conservatively without leaving any ocular deformity in a follow up period of 2 week. At time of admission 2 patient show 6th CN Palsy, these two patient also have Papilloedma. 6th cranial nerve palsy is a pseudo localizing sign in Papilloedma which resolve as the ICT lower down or Papilloedma resolves. But in these patient Papilloedma resolve in a month period but 6th nerve does not come to its normal level. Thus producing a major neurological deficit in these children. Raised ICT can result in downward displacement of brainstem, causing stretching of the 6th cranial nerve which leads to 6th CN palsy. At time of admission 12 children show Papilloedma. On 2nd day of admission number of children showing Papilloedma remain same and in 1 week follow up of admission 11 children show Papilloedma. Papilloedma is seen more in unconscious children. Only 1 children of normal GCS show Papilloedma and the rest 11 children show Papilloedma were of GCS <15. Out of them 1 children were GCS 14-12, 3 children were of GCS 12-9, 5 children were of GCS 9-7 and 2 children were of GCS <7. Showing that Papilloedma is more common in children having lower level of consciousness i.e. the children severely ill. In post discharge patient at 1 week 11 children show Papilloedma, at 1 month follow up 8 children show Papilloedma, at 3 month period 2 children show Papilloedma and at 6 months period 2 children show Papilloedma with post oedema optic atrophy. Papilloedema in AES may be because of the axoplasmic stasis, oedema or vascular congestion due to generalized body viremia. Ocular manifestation of Vitamin A deficiency is seen in 13 children (6 male, 7 female) 6 children come in XN grade (3 male, 3 female), 2 children come in X1A grade (1 male 1 female), 3 children in X1B grade (1 male, 2 female), 1 children in X2 grade (1 female) and I children in X3A grade (1 male). So total of 8.7 % male population of AES show vitamin A deficiency while 14.29% of female population show the deficiency. This show that vitamin deficiency is more common in female children as compared to male population and most of patients belong to rural background.

For neurological manifestation and behavioural problem all children underwent a detailed examination by a paediatrician. Children which show a complete recovery from AEs in follow up patient were 74 i.e. 62.71% population .Behavioural problem with no neurological deficit is seen in 3 children (2.54%), minor neurological deficit is seen in 10 children (8.47%) , minor neurological deficit with behavioural problem in 6 children (5.08 %), major neurological deficit in 13 children (11.02 %) and major neurological deficit with behavioural problem in 10 children (8.47%). So total children showing behavioural problem (with or without minor or major neurological deficit) seen in 19 children (16.02%). Total major neurological (including major neurological deficit with behavioural problem) seen in 23 children i.e. 19.40 %. Major neurological deficit include impaired memory in 4 children (17.39%). Out of 118 patients 96 children recover without leaving any ocular deformity i.e. 81.35% children in a follow up period of 6 months. Total number of children showing untreatable blindness in our study were 18 (10 male, 8 female) .Causes of untreatable blindness are post oedema optic atrophy in 2 children (1 male , 1 female) and retro bulbar neuritis / higher cortical lesion in 16 children (9 male, 7 female). 2 children show nebular / macular grade corneal opacity with visual acuity near normal. 2 children show 6th Cranial Nerve palsy without recovery in a follow up period of 6 month.

Conclusions

Various observations in our study have clearly indicated that AES is more common in young males in rural area. Children showing ocular finding were 44 i.e. 37.29% of total population and the remaining 74 children i.e. 62.71% population does not show any ocular finding. Ocular manifestation of Vitamin A deficiency is seen in 13 children (6 male, 7 femal). Children showing untreatable blindness in our study were 18 (10 male, 8 female). Causes of untreatable blindness are post oedema optic atrophy in 2 children (1 male, 1 female) and retro bulbar neuritis / higher cortical lesion in 16 children (9 male, 7 female). So 15.25 % treated population suffer visual disability. 2 children show 6th Cranial Nerve palsy without recovery in a follow up period of 6 month. 2 children show nebular/macular grade corneal opacity. Major neurological (Major neurological deficit and major neurological deficit with behavioural problem) seen in 23 children i.e. 19.40 %. So total children showing behavioural problem (with or without minor or major neurological deficit) seen in 19 children (16.02%). Out of 118 patient 96 children recover without leaving any ocular deformity i.e. 81.35% children in a follow up period of 6 month. Children which show a complete recovery from AES (without leaving any neurological deficit and behavioural problem) in follow up patient were 76 i.e. 64.41% population . So ocular damage and blindness is quiet common in AES. All children should underwent a thorough ophthalmological examination and follow up.

References

1. Rantala H, Uhari M. Occurrence of childhood encephalitis: a population- based study Paediatrictr Infect Dis J 1989; 8:426-430.
2. CMDT. Infectious disease: viral and Ricketsial. 2005. p.1340-1341.
3. Abzug MJ,Loeffelholz M and Robart HA.Diagnosis of neonatal enterovirus infection by polymerase chain reaction.J Pediatr.1995; 126:447-450.
4. WHO-recommended standards for surveillance of selected vaccine-preventable diseases. (http://www.who.int/vaccines-documents/DocsPDF06/843.).
5. Acute flaccid paralysis surveillance systems for expansion to other diseases, 2003–2004 MMWR Morb Mortal Wkly Rep 2004.
6. Beghi E, Nicolosi A, Kurland LT: Encephalitis and aseptic meningitis, Olmsted County, Minnesota, 1950–1981: I. Epidemiology. Annals of Neurology 1984; 16:283.
7. David Greenwood, Richard Jonn. Medical microbiology: a guide to microbial infection, pathogenesis. Immunity,Lab diagnosis and control. 15th ed., p 450-460.
8. Farmer KG, MacArthur A and Clay MM. A follow-up study of 15 cases of neonatal meningoencephalitis due to Coxsackie virus b5. J Pediatr. 1975; 87:568-571.
9. Berlin LE,Rorabough ML,Heidrich F, Roberts K, Koran and Modlin.Aseptic meningitis in infants <2 years of age:diagnosis and etiology.J Infect Dis.1993; 168:888-892.
10. Clen C , Mayhall,Lipincotts,William and Wilkins. Hospital epidemiology and infection control.3rd ed.p.865-868.
11. Bopegamage SA,Petrovicova A,Stara M.Detection of Cocsackie B virus infection using rapid screening method.
12. Gravanis MG and Sternby NH. Incidence of myocarditis. Arch Fathol Lab Med. 1991; 115:390-392.
13. Gow JW, Behan WM, Clements GB, Woodall M Riding and Behan PO. Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome. Br Med J. 1991; 302:692-698.
14. Gatmaitan BG, Chason JL and Lerner Am. Augmentation of the virulence of murine Coxsackie virus B-3 myocardiopathy by exercise. J Exp Med. 1970; 131:1121-1136.
15. Brennan FH Jr.et al.Diagnosis and management of myocarditis in atheletes.Curr Sports Med Rep.2003; 2:65.
16. Brunner J, Litwicki A, Aliani S, Gartner B. Coxsackie virus B and encephalitis in a 7 years old boy:a case report. Department of Pediatrics, University of Sarrland, Homburg/scar,Germany.
17. Ponka A, Pettersson T: The incidence and aetiology of central nervous system infections in Helsinki in 1980. Acta Neurologica Scandinavica 1982; 66:529-53
18. Kamei S, Takasu T: Nationwide survey of the annual prevalence of viral and other neurological infections in Japanese inpatients. Intern Med. 2000; 39:894-900.
19. Cherry JD and Jahn CL.Herpangina:the etiologic spectrum. Pediatrics. 1965; 36:632-634.
20. Douglas D Richman,Richard J,Frederick G Heyden et.al. Clinical virology 2nd ed,p.971-981.
21. Ishikawa T, Asano Y, Morishima T, Nagashima M, Sobue G, Watanabe K, Yamaguchi H: Epidemiology of acute childhood encephalitis. Aichi Prefecture, Japan, 1984–90. Brain Dev 1993, 15:192-197.

22. Clernents GB, Galbraith DN and Tayor KW.Coxsackie B virus infection and onset of childhood diabetes. Lancet.1995; 346:221-223.

23. Klemola E, Kaeaeriaeinen L, Ollila O, Pettersson T, Jansson E, Haapanen L, Lapinleimu K, Forssell P: Studies on viral encephalitis. Acta Med Scand. 1965, 177:707-7.

24. Solomon T, Thao TT, Lewthwaite P, Ooi MH, Kneen R, Dung NM, White N: A cohort study to assess the new WHO Japanese encephalitis surveillance standards. Bull World Health Organ. 2008; 86:178-186.

25. Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P: Etiology of aseptic meningitis and encephalitis in an adult population. Neurology. 2006; 66:75-80.