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Abstract

Objective: To devise a set of clinical signs and laboratory parameters that would help clinicians assess prognosis in patients and plan appropriate management.
Methods: Medical records of 147 paediatric cases (with a discharge diagnosis of acute viral encephalitis) admitted over a ten year period from 1987 to 1997 were reviewed and relevant information collected on a data extraction form.
Results: Of 147 patients, 24 (16.3%) died and 48 (32.7%) were left with severe neurological deficits. A GCS (Glasgow Coma Scale) score between 6-10 had an association with poor outcome (OR = 2.62, Chi-square = 5.57, p-value = 0.018) and that a GCS score of >5 was even more strongly suggestive of poor outcome (OR = 5.49, Chisquare = 12.08, p-value =0.0005). A history of having seizures, for more than 3 days, also showed a strong association with poor outcome (OR= 3.66, Chi- square = 5.46, p-value = 0.019).
Conclusion: Patients with an increased risk of death and severe disability can be identified using a few guidelines. Of these, a history of seizures of >3 days and/or impaired consciousness (GCS _10), at the time of presentation to the hospital, constitute high risk. These cases must be identified promptly and aggressive therapy initiated in order to improve long term outcome OPMA 49:311,1999).

Introduction

Central Nervous System (CNS) infections have tremendous importance because of their potential for death and permanent neurological damage. The reported incidence of acute encephalitis is between 3.5-7.5 cases per 100,000 patient years[1]. In children the incidence is about 16.7 cases per 100,000 patient years[2]. Acute encephalitis occurs most commonly in the first decade of life with a peak incidence of 1-2 cases per 1000 in the first 6 months of life[3]. The mortality rate of children with acute encephalitis is 3.8- 28.0%[4]. Study done in American paediatric population, showed that 40% of children who recovered from acute encephalitis had persistent non-progressive neurological abnormalities[5]. Several studies have been done to find clinical parameters that could predict poor outcome, one such study done in U.K. showed clinical predictors as young age at presentation, alow score on the Glasgow Coma Scale (GCS), disruption of the occulocephalic response and laboratory evidence of infection in the CNS[6]. In a study on 462 Finnish children[4], the risk of death or severe damage in children less than one year of age was five-fold greater than that of older children. There was a 3.9% greater risk of death or severe damage in those children who had been disoriented on admission versus those who were not. In addition those children with Herpes Simplex Virus (HSV) or Mycoplasma pneumoniae type encephalitis had greater risk (11.7 fold and 7 fold respectively) of death or severe damage versus those of other viral aetiologies. In another paediatric study focal neurological signs and abnormal neuroimaging studies were the only two factors that predicted poor short-term outcome[7]. The GCS was only predictive if profoundly depressed (<6) but was otherwise not useful.
The impact of acute viral encephalitis on individuals and families can be devastating. As timely intervention can be life saving, the aim of this study was to determine the clinical signs and laboratory

parameters that could help assess high risk cases of viral encephalitis in our local setting.

Patients and Methods

The study was conducted at The Aga Khan University Hospital (AKUH), Karachi. A retrospective review of records was performed using a pre-tested data extraction form. We included all paediatric cases aged <15 years, admitted during the 10 years between 1987-1997, who presented within one month of symptom onset and had a diagnosis at discharge of viral encephalitis[4]. For the ten years period of observation, a final study population of 147 was reached.

The data extraction form was constructed based on criteria laid out by Western literature[4-7], a study conducted in India[8] as well as in-house neurologists. It collected relevant information on demographics, signs and symptoms at presentation, laboratory and radiological investigations done, treatment given and outcome recorded (both at discharge and at follow up within 6 months). Outcome was expressed in four categories which ranked from 1-4 as follows: 1 = death, 2 = major neurological sequelae, 3 = minor neurological sequelae, 4 complete recovery with no deficits. Major sequelae included seizures, frank motor deficits (increased tone, hemiplegias, monoplegias, cerebellar signs, lower motor neuron signs, extrapyramidal signs), cranial nerve damage, mental retardation[8]. Minor sequelae were scholastic backwardness, subtle neurological signs (up-going plantars, in-coordinate or brisk reflexes) and behavioural changes[8]. For the purpose of analysis death and major sequelae were regrouped as 'poor outcome' whereas minor sequelae and recovery were called 'favourable outcome'. EPI Info version 6.0 statistical package was used for data analysis. Poor outcome (n=72) was compared with favourable outcome (n=75) in terms of clinical variables like symptoms, signs, laboratory values, radiology and treatment at admission. Age was grouped into discrete categories (il, 2-5, 6-10 and 11-15 years), as was duration of symptoms (<3, 4-7 and >7 days) and GCS (<5, 6-10 and 11-15). All other values were grouped as abnormal or normal based on hospital set protocol. Chi-square analysis was used to determine presence of association and odds ratio calculated for significant results. Results were considered significant if p-value was <0.05.

Results

A total of 147 cases fullfilled our case definition, of these 42 (28.8%) were females and 104 (71.2%) male. No age group dominated. Acute encephalitis was not associated with any particular season. The most common symptoms at presentation were fever in 114 (77.5%), impaired consciousness in 83 (56.5%) and seizures in 81(55.1%) cases. Sixty-nine (52.3%) had a GCS of 11-15 at presentation (Table 1).

Table 1. Characteristics of the study population.

Variables	n	%	Variables	n	%
Age			Recent history of		
<1 years	37	25	Rash	37	25
2-5 years	49	33	Respiratory tract infections	37	25
6-10 years	44	30	GIT infections	14	10
11-15 years	17	12	Vaccination[S]	7	5
Total	147	100			
Gender			Family History of		
Female	42	29	Seizures	12	8
Male	104	71	Neurological illness	4	3
Total	146	100	Psychiatric illness	0	0
Season at presentation			History of chronic illness		
Feb/Mar/Apr	38	26			
May/Jun/Jul	42	28	Neurological	17	12
Aug/Sep/Oct	37	25	Others	7	5
Nov/Dec/Jan	29	20			
Total	146	100			
Hospital stay			Glasgow coma scale		
<3 days	38	26	≤5	25	19
4-7 days	44	30	6-10	38	29
8-14 days	43	29	11-15	69	52
>15 days	22	15	Total	132	100
Total	147	100			
Symptoms*			Treatment		
Fever	114	78	Acyclovir given	39	27
Impaired Consciousness	83	57	Acyclovir not given	108	73
Seizures	81	55	Total	147	100
Vomiting	45	31			
Behavioural changes	20	14			

* Total = 147 for each variable under his category

+ Within 2 weeks prior to presentation

[S] Measles, Mumps, Rubella, Chicken Pox

Documentation of physical signs were missing in many files and highly variable in the remaining ones; therefore these could not be assessed.

None of the haematological investigations revealed any significant trend (Table 2).

Table 2. Finding of laboratory and other investigations.

Variables	Normal		Abnormal					
			Low		Raised		Not Raised	
	n	%	n	%	n	%	n	%
LABORATORY FINDINGS								
SERUM								
Sodium* [136-148 mmol/L]	100	73	35	26	2	1	-	
TLC+[4-10x10^9/L]	-		-		57	40	86	60
DLC*								
Polymorphs [40-75%]	-		-		26	19	111	81
Lymphocytes [20-45%]	-		-		37	27	100	73
CSF								
CSF RBC^s [0/µL]	-		-		103	91	10	9
CSF TLC** [0-6/µL]	-		-		48	41	70	59
CSF DLC++								
Polymorphs	-		-		8	17	-	
Lymphocytes	-		-		38	83	-	
CSF Proteins**[15-45 mg/dl]	71	60	21	18	26	22	-	
CSF Glucosess[50-75 mg/dl]	70	60	10	9	37	31	-	

*n = 137 ^{s}n = 114 ++n = 46
+n = 143 **n = 118 ^{ss}n = 117

Serum sodium was normal in 72.5% cases. Cerebrospinal fluid (CSF) examination was not done in 29 (19.7%) cases. In the remaining cases CSF analysis revealed abnormal leukocyte counts in 40.7%. Lymphocytosis was found in 82.6% cases in which a CSF Differential Leukocyte count (DLC) was performed. Sixty percent of CSF protein levels fell within the normal range as did CSF glucose levels (60% cases). Of the cases in which CSF culture and sensitivity was performed, 98% showed no growth. Electroencephalogram (EEG) was performed in 89 cases of which 86 (96.6%) had abnormal findings and CT scan was performed in 83 cases, of which 45 (54.2%) showed abnormalities. Acyclovir was administered in 39 patients (27%). Mean hospital stay was of 9.3 days, with 82 (55.8%) staying for a week or less and 125 (85%) being discharged within two weeks (Table 1).

Of 147 cases, 24 (16.3%) died. For the remainder at discharge, 48 (32.7%) had major sequelae, 19 (12.9%) had minor sequelae and 56 (38.1%) recovered completely. Of the major sequelae seen, the commonest was motor deficits in 26 followed by seizures in 14 . The more common minor sequelae seen at discharge were subtle neurological defects in 11 and behavioural changes in 3. Of those who died, 5 (20.8%) had complicating systemic diagnoses but this was not statistically significant. Follow up records were not available for 62 (50.4%) cases. In those who came for follow up, major sequelae were found in 16 (26.2%) patients and minor sequelae in 13 (2 1.3%) patients (Table 3).

Table 3. Clinical Sequelae at discharge and follow up (within 6 months).

	N	n	%		N	n	%
Sequelae at discharge				Sequelae at follow up*			
Death		24	16	Death		1	2
Major sequelae		48	33	Major sequelae		16	26
Seizures	14			Seizures	6		
Motor Deficits	26			Motor Deficits	10		
Cranial nerve palsies	4			Cranial nerve palsies	2		
Mental retardation	5			Mental retardation	4		
Others	9			Others	0		
Minor sequelae		19	13	Minor sequelae		13	21
Subtle neurological deficits	11			Subtle neurological deficits	6		
Scholastic Backwardness	1			Scholastic Backwardness	2		
Behavioural changes	3			Behavioural changes	4		
Others	25			Others	3		
Complete Recovery		56	38	Complete Recovery		31	51
Total		147	100	Total		61	100

*Sixty-two (50%) patients were lost to follow up.

For ease of analysis we combined the groups death and major sequelae as poor outcome and minor sequelae and complete recovery as favourable outcome. No significant association of outcome was found with age at presentation (Chi-square = 3.99, p-value = 0.26) or season at presentation (Chi-square = 1.00, p-value = 0.80). A GCS score of 6-10 was significantly associated with poor outcome (OR=2.64, Chi-square=5 .57, p-value=0.0 182). There was a significantly worsening prognosis as GCS fell below 5 (OR = 5.49, Chi-square = 12.08, p-value = 0.0005) and the Chi-square for this linear trend was significant (p-value 0.00025). Of the presenting symptoms, a history of seizures for >7 days, although showing a strong association with poor outcome (one-tailed Fisher exact p-value = 0.011), failed to generate an Odds ratio due to the fact that no patient presenting with such a prolonged duration had a favourable outcome. To overcome this the duration of symptoms were regrouped into two categories of <3 and >3 days and the Odds ratio recalculated. The result then showed that a history of seizures of >3 days duration suggested poor outcome (OR = 3.66, Chisquare=5.46, p-value = 0.0 19) (Table 4).

Table 4. Association of outcome at discharge with various clinical parameters.

Clinical parameters	n	%	Outcome		Odds Ratio (Confidence Interval)	χ^2	p-value
			Poor	Favourable			
AGE (Total = 147)							
≤1 year (Ref.)	37	25.2	20	17	1.00	-	-
2-5 years	49	33.3	28	21	1.13 (0.44-2.93)	0.08	0.775
6-10 years	44	29.9	17	27	0.54 (0.20-1.42)	1.93	0.165
11-15 years	17	11.6	7	10	0.60 (0.16-2.20)	0.77	0.379
SYMPTOMS (Total = 147)							
Fever*	114	77.5	53	61	0.65 (0.27-1.50)	1.26	0.262
Impaired Consciousness*	83	56.5	43	60	1.30 (0.64-2.63)	0.61	0.435
Seizures*	81	55.1	44	37	1.61(0.80-3.28)	2.06	0.151
Vomiting*	45	30.6	19	26	0.68 (0.31-1.45)	1.19	0.276
Behavioural changes*	20	13.6	7	13	0.51 (0.17-1.50)	1.81	0.179
SEIZURE PRESENTATION (Total=81)							
≤3 days(Ref.)	60	74.1	28	32	1.00	-	-
>3 days	21	25.9	16	5	3.66 (1.07-13.22)	5.46	0.019 ι
GLASGOW COMA SCALE (Total=132)							
≤5	25	18.9	18	7	5.49 (1.82-17.16)	12.08	<0.01 ι
6-10	38	28.8	21	17	2.64 (1.08-6.49)	5.57	0.018 ι
11-15 (Ref.)	69	52.3	22	47	1.00	-	-
EEG (Total = 89)					∞	-	0.086+
Abnormal	86	96.6	49	37			
Normal (Ref.)	3	3.4	0	3	1.00	-	-
CT SCAN (Total = 83)							
Abnormal (Ref.)	45	54.2	27	18	1.09 (0.41-2.08)	0.04	0.846
Normal	38	45.8	22	16	1.00	-	-
ACYCLOVIR (Total = 147)							
Given	39	26.5	18	21	0.86 (0.39-1.90)	0.17	0.680
Not given (Ref.)	108	73.5	54	54	1.00	-	-

Ref. = Reference category

*For each, absence of symptom has been taken as the Reference category

+Fisher exact p-value (one-tailed)

ι Statistically significant at p<0.05

Hyponatremia was not found to have any relation with outcome (OR=1.10, Chi square=0.06, p-value=0.81), neither did CSF lymphocytosis (OR=5.09, Chi-square=2.49, p-value=0.115) nor CSF protein (OR=l.39, Chi-square=0.55, p-value=0.46). Despite the fact that EEG abnormalities were present in 96.6% tested cases, no significant association with outcome could be established (one-tailed Fisher exact p-value=0.086). CT abnormalities also failed to show an association with outcome (OR=1.09, Chi-square=0.04, pO.846) (Table 4). The administration of acyclovir did not affect outcome (OR=0.86, Chi square0.17, p=0.68) (Table 4).

Of the patients who did have a follow up record in their file, a strong association was found between poor status at discharge and poor status at follow up (0R72.00, Chi-square=29.63, p

Discussion

In this study we have taken viral encephalitis caused by infection with any one of several common viruses as one entity. Although this does not take into account the pathogenesis of individual etiological agents this study has the advantage of being applicable in our setting where sophisticated investigations for causative organisms are not carried out.

Previous studies have shown conflicting views regarding the age at presentation and outcome. Our finding was that age at presentation had no relation with the prognosis. This is in accordance with Klein et al.[7] but differs from Rautonen et al.[4] and Kennedy et al.[6] who found a significantly worse prognosis in those aged <3 and <1 years respectively. Seasonal variation has been seen to have a relation with the onset of viral encephalitis, being more in winter and early spring in the west and following the monsoon season in Lucknow, India[8]. However, no such correlation was found in this study, but this could be due to the absence of well-defined seasons in this part of the sub-continent.

The most common clinical presentations were fever, impaired consciousness, seizures, vomiting, behavioural changes, recent rash and a recent history seizures of respiratory infections. Out of these, history of with an onset of greater than 3 days, showed an association with poor outcome. Rautonen et al.[4] correlated the duration of symptoms with outcome in their study among Finnish children but were unable to get results that were statistically significant.

One of the most important findings in this study was that those patients with a score of<5 on the Glasgow Coma Scale had a significantly worse prognosis than those with a higher score. This is in accordance with previous studies, especially those of Kennedy et al.[6] and Klein et al.[7] We, however, also showed that the prognosis was poor even for a relatively higher score of 6-10 and as GCS fell below this the prognosis deteriorated concurrently. Abnormal occulocephalic reflexes have a very strong correlation with unfavourable outcome[6]. Unfortunately due to lack of adequate documentation we were unable to assess this parameter. Previous studies have contemplated the relationship between CSF findings and outcome. However no significant associations have been established which is in agreement with our findings.

Two other diagnostic modalities analysed were the CT and the EEG. Magnetic Resonance Imaging (MRI) has only been recently introduced at our hospital and therefore this investigation was excluded from our analysis. EEG picked up abnormalities in 97% cases compared with CT which picked up abnormalities in 54% (Table 2). In both these cases, however, no statistically significant association with outcome could be established.

The antiviral drug Acyclovir is used in Herpes Simplex Virus (HSV) encephalitis and if administered early drastically improves the course of this potentially fatal illness. In our analysis Acyclovir administration had no relation with outcome. However, the role of this drug cannot be assessed from this finding as we did not stratify for HSV.

At the time of discharge 49% of patients either died or had major sequelae. This is in contrast with Rautonen et al.[4] in which 9.5% of cases died or had severe damage. This discrepancy could be explained by differences in race, etiological agent, the duration of the illness at which the patient presented and the inability of the family to afford tertiary care resulting in the patient being discharged once stabilised (not cured) i.e., before optimum therapy. The latter limitation would make the patient appear worse off than those admitted for a longer period. To overcome this bias it would have been ideal to have documentation of a follow up visit. Unfortunately follow up records were not available for half of the cases. However it was seen that in those with a follow up there was a significant correlation with poor status at discharge and subsequent follow up. Similarly those with a favourable outcome on discharge maintained a good status on follow up.

We conclude that increased rate of death and severe damage in encephalitis can be identified by a few basic factors. Specific attention should be focused on those cases that present with a history of seizures

of >3 days duration prior to admission and especially those which have presented with impaired consciousness. Being a pilot study we recommend that more research should be directed towards viral encephalitis and other acute central nervous system infections.

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References

1. Johnson RT. Acute Encephalitis. Clinical Infectious Diseases, 1996;23:219-26.
2. Koskiniemi M, Rautonen J, Lelitenierni E, et aI. Epidemiology of encephalitis in children: A 20 year survey. Annals of Neurology. 199129:492-97.
3. Wang D, Bertolussi R. Acute viral infections of the central nervous system: An 8 year review. J. Can. Med. Assoc., 1981:125:585-89.
4. Rautonen J, Koskiniemi M. Prognostic factors in childhood acute encephalitis. Paediatric Infectious Disease Journal. 1991:10:441-46.
5. Doachowske JB. Acute manifestation and neurological sequelae of EBV encephalitis in children. The J. Paed. Infect. Dis., 1996:15:871-75.
6. Kennedy C, Duffy S, Smith R, et al. Clinical predictors of outcome in encephalitis. Archi. Dis. Child., 1987:62:156-62.
7. Klern SK. Predictive factors in short term neurological outcome in children with encephalitis. Paed. Neuro., 994:11:308-12.
8. Kurnar, Rashmi et al. Clinical sequelae of Japanese encephalitis in children. lnd. J. Med. Res., 1993,97:9-13.