Acyclovir-Induced Nephrotoxicity in Adults with Viral Encephalitis

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ABSTRACT

Objective: To determine the frequency of parenteral Acyclovir-induced Acute Kidney Injury (AKI) in patients with viral encephalitis.
Study Design: Descriptive study.
Place and Duration of the Study: Department of Neurology, Liaquat National Hospital, Karachi, from January to December 2021.
Methodology: A total of 89 suspected and proven cases of encephalitis receiving IV Acyclovir were collated. All had extensive medical histories and underwent CSF studies with +/- brain imaging. CSF routine and viral PCR were done. Acyclovir-induced AKI was defined as a rise in serum creatinine of >0.3 mg/dl in 48 h or by ≥1.5 times the baseline value, and its severity was staged into 1 (risk), 2 (injury), and 3 (failure) according to the KDIGO guidelines (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Patients' variables, including age, gender, presenting features, comorbid conditions, and CSF findings, were divided into two groups, i.e. with and without AKI.
Results: This research included 89 patients with a mean age of 48 years. AKI occurred in 34 patients (38.2%). The frequency of AKI with Stage 1 was 24%, Stage 2 was 44%, and Stage 3 was 32%; approximately two-thirds of cases were in Stage 2 and 3 (p >0.05). Five patients (5.6%) from Stage 3, required dialysis.
Conclusion: AKI is an important adverse effect of parenteral acyclovir, which necessitates its early identification and timely management. Renal function monitoring is essential for patients on Acyclovir treatment as they are at risk for AKI.

Key Words: *Acyclovir, Acute kidney injury, Viral encephalitis, Creatinine, Kidney Disease Improving Global Outcomes.*

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INTRODUCTION

Encephalitis is an inflammation of the brain parenchyma that is most commonly viral in origin. The most common virus reported for sporadic, non-epidemic encephalitis in both children and adults is the *Herpes simplex* virus (HSV).[1] A suspected case of viral encephalitis is diagnosed using a combination of the clinical judgment and certain laboratory parameters. This includes diagnostic tests on cerebrospinal fluid (CSF), specific confirmatory polymerase chain reaction (PCR) studies for viral agents, electroencephalograms (EEG), and MRIs of the brain that may show characteristic or nonspecific findings. The results of viral studies are reported in ≥2 days, which may not be available in many centres. Clinical judgment remains essential for making timely decisions about an urgent antiviral treatment for this disease, as it is a very serious condition with 70% mortality if left untreated.[2-4]

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Early initiation of therapy also results in maximal therapeutic benefit. The recent guidelines suggest treating viral encephalitis empirically with Acyclovir on the clinical grounds.[5]

A synthetic guanine nucleoside analogue known as Acyclovir has potent antiviral action against HSV and other *Herpes* viruses that are related to HSV-causing encephalitis.[6] Acyclovir is relatively a safe and well-tolerated drug, but it has the potential to cause AKI.[7] Since the main route of elimination is renal, dosage adjustments may be necessary for patients with renal insufficiency. The patho-mechanisms by which it causes AKI are acute interstitial nephritis and crystal nephropathy.[8,9] Severe nephrotoxicity with acute renal failure has been reported in patients.[10,11] In Pakistan, there is a scarcity of literature on adults; however, few studies are available in the paediatric age group regarding Acyclovir-induced AKI.[12,13] The objective of this study was to determine the frequency and severity of Acyclovir-induced AKI in adults with viral encephalitis.

METHODOLOGY

This descriptive, cross-sectional research was carried out at the Neurology Department of Liaquat National Hospital, Karachi, Pakistan, from January to December 2021. The inclusion criteria was viral encephalitis patients presenting with clinical features (altered sensorium, with/out neurological deficit)

supported by CSF biochemical, specific viral PCR studies, and neuroimaging studies. Cases of either gender with an age ≥14 years were enrolled through non-probability convenience sampling with one serum creatinine measurement at the baseline and 48 hours. Patients who were aged <14 years and had a history of any underlying renal disorder and patients with a hospital stay of <48 hours were excluded from the study.

The sample was estimated on the Open-EPi online calculator by taking a 95% confidence interval, a 7% margin of error, and a 13% frequency of AKI in adults receiving intravenous Acyclovir.[14] Data of 89 suspected and proven cases of encephalitis receiving Acyclovir were collated. The clinical diagnosis was suspected in any patient who presented with acute-onset fever and altered sensorium, with and without focal neuralgic findings; all had extensive medical histories and underwent CSF ± brain imaging. The CSF routine was tested and the CSF for viral identification was done using a real--time PCR machine.

Patient demographic data (gender, age) and comorbidities including hypertension, Diabetes mellitus (DM), malignancy, and chronic kidney disease (CKD) were collected. The known nephrotoxic medicines (NSAIDs, diuretics, ACI, ARBS) were withheld. AKI was defined per KDIGO (2012) guidelines, as a rise in serum creatinine of at least 0.3 mg/dl over 48 hours (criteria 1), or a rise of at least 1.5 times the baseline value in serum creatinine (criteria 2), or urine output <0.5 ml/kg/h for >6 hours (criteria 3). AKI severity was staged into risk (stage 1), injury (stage 2), and failure (stage 3) according to KDIGO serum creatinine criteria.[15] Serum creatinine levels were used as a measure of AKI in this study. A baseline serum creatinine was determined at the time of admission and repeated 48 hours after the initiation of Acyclovir therapy. If there was evidence of AKI on the repeat creatinine, the dose was either reduced or stopped (in severe cases). Adequate hydration was ensured for patients who developed acute renal failure and dialysis was performed on some cases, as required. The study participants receiving Acyclovir for viral encephalitis were grouped into two categories, i.e. one with AKI and the other without AKI. Additionally, they were compared on four sets of variables, which included demography, clinical features, CSF analysis, and neuroimaging, to determine their role, if any, in Acyclovir-induced nephrotoxicity.

Data were entered in SPSS version 23 for the statistical analysis. Frequency and percentage were computed to summarise the qualitative variables. The numerical variables were first assessed for normality assumption using the Shapiro-Wilk test. The median and interquartile range were used to indicate variables that were not normally distributed. The categorical features of patients were compared between those who developed and did not develop AKI using the Chi-square or Fisher's exact test. Non-normally distributed numerical variables between the two groups were compared by applying the Mann-Whitney U test. A p-value of 0.05 or less was considered statistically significant.

RESULTS

The research included 89 patients. Table I displays the descriptive statistics for patients' characteristics and the comparison with and without AKI. The patients had a median age of 48 years (age range of 14-81 years) with a male predominance of 60.7%. The presenting features were altered sensorium with GCS <7 (84.3 %), seizures (24.7%), and focal neurological findings (11.2%). Out of 32 patients (36 %) who had comorbidity, 18 (56.3%) had hypertension, 11 (34.4%) had Diabetes, 3 (9.4%) had a stroke, and 1 (3.1%) each had malignancy, hypothyroidism, epilepsy, ischaemic heart disease, hepatitis C, and asthma.

Table II displays the comparison of CSF analysis and serum baseline creatinine levels amongst the two groups of patients who developed or did not develop AKI.

Table I: Comparison of patient characteristics, clinical features, and comorbidities of patients with and without AKI.

Patients' characteristic	Total n (%)	With AKI n (%)	Without AKI n (%)	p-value
Age groups				
≤20 years	10 (11.2)	3 (30)	7 (70)	0.594
21-39 years	21 (23.6)	6 (28.6)	15 (71.4)	
40-59 years	40 (44.9)	18 (45)	22 (55)	
60 years and above	18 (20.2)	7 (38.9)	11 (61.1)	
Gender				
Male	54 (60.7)	18 (33.3)	36 (66.7)	0.240
Female	35 (39.3)	16 (45.7)	19 (54.3)	
Presenting features				
GCS* score <7	75 (84.3)	30 (40)	45 (60)	0.419
Generalised or partial seizures	22 (24.7)	8 (36.4)	14 (63.6)	0.838
Focal neurologic findings	10 (11.2)	6 (60)	4 (40)	ǂ0.172
Comorbid				
Yes	32 (36)	13 (40.6)	19 (59.4)	0.724
No	57 (64)	21 (36.8)	36 (63.2)	
Hypertension	18 (20.2)	6 (33.3)	12 (66.7)	0.634
Diabetes	11(12.4)	3 (27.3)	8 (72.7)	ǂ0.521

*ǂ Fisher-exact test is reported, * Significantly different at p<0.05 *GCS: Glasgow Coma Scale.*

Table II: Comparison of CSF and baseline serum creatinine of patients with and without AKI.

Patients' characteristic	Total n (%)	With AKI n (%)	Without AKI n (%)	p-value
CSF DR				
White blood cell count# (in cell/mm^3)	115 (25-400)	122.5 (23.7-382)	110 (25-480)	0.797
Neutrophils#	10 (10-10)	10 (10-10)	10 (10-10)	0.073
Lymphocytes#	90 (90-90)	90 (90-90)	90 (90-90)	0.139
Protein# (in mg/dl)	126 (68-161)	134 (65.7-169)	121 (68-158)	0.899
Sugar# (in mg/dl)	66 (50.5-86.5)			0.598
Creatinine at baseline# (in mg/dl)	0.8 (0.6-1)	0.8 (0.7-1.02)	0.8 (0.6-1)	0.434
Female	35 (39.3)	16 (45.7)	19 (54.3)	

#: Data presented as median with inter-quartile range and compared using Mann-Whitney U test.

Table III: Frequency distribution for the laboratory parameters: Findings of CSF viral PCR, EEG, and neuroimaging.

Findings	Frequency (%)
CSF* viral PCR	
Not detected	29 (32.6)
EBV	18 (20.2)
HSV	17 (19.1)
VZV	13 (14.6)
Human adenovirus	4 (15.7)
CMV	1 (1.1)
EEG#	
Not done	45 (50.6)
Normal	31 (34.8)
Epileptic discharge	10 (11.2)
Diffuse axonal dysfunction	3 (3.4)
Neuroimaging	
Not done	40 (44.9)
Normal	44 (49.4)
Leptomeningeal enhancement	3 (3.4)
Herpes encephalitis	1 (1.1)
High-intensity signals	1 (1.1)

** CSF: Cerebrospinal fluid, EBV: Epstein–Barr virus, HSV: Herpes simplex virus, VZV: Varicella zoster virus, CMV: Cytomegalovirus, #EEG: Electroencephalogram*

None of the patients' features, including age, gender, presenting features, hypertension, diabetes, and creatinine levels at the baseline and 48 hours were significantly different among those who developed AKI and those who did not.

Using the KDIGO classification of renal impairment, AKI Stage 1 was observed in 24% of cases, Stage 2 in 44%, and Stage 3 in 32% of cases, indicating that approximately 2/3rd of the cases were stage 2 and 3. Out of 89 patients, five patients (5.6%) required renal replacement therapy in the form of dialysis.

Table III shows the findings of CSF viral PCR, EEG, and neuroimaging. The PCR virology was positive in 70 cases. The most common pathogens were EBV (20.2 %), HSV (19.1%), and VZV (14.6 %). Abnormal results of EEG and neuroimaging were noted in a limited number of patients.

DISCUSSION

AKI is characterised by an abrupt decline in renal functions, which include impaired excretion of waste products and dysregulation of fluid, electrolytes, and acid-base homeostasis. The rate of Acyclovir-associated AKI in patients with viral encephalitis in the current study was 34%. This finding correlated with the previous reports highlighting that AKI occurred in 12–48% of the cases.[11]

Acyclovir-induced nephrotoxicity is a dreadful but preventable complication that poses a great risk to hospitalised patients. Reduced renal function is the hallmark of (AKI) due to Acyclovir, which typically manifests within 12 to 48 hours of drug administration. Since Acyclovir does not compete with creatinine for tubular excretion like other antivirals do,[16] the increase in serum creatinine observed is a real indication of renal damage. The serum creatinine levels of the patients in this study also started to rise within 48 hours of receiving IV Acyclovir therapy, providing evidence of this trend.

In the present study, approximately two-third cases were in Stage 2 and 3, indicating that Acyclovir-associated AKI was clinically significant. This was comparable to study with similar results, in which two-third cases were Stage 2 and 3.[14] Dialysis was needed in some severe cases,[17] as observed in this study. Stage 1 of AKI is usually transient, while Stage 2 and 3 have more severe short-term and long-term outcomes.

The patients' demographics, clinical features, and laboratory parameters were compared in the two sets of patients, i.e. with and without AKI. The nephrotoxicity was not influenced in these patients. The probable explanation was that it could be an idiosyncratic reaction associated with the use of IV Acyclovir, as some individuals showed an abnormal susceptibility to Acyclovir. Inadequate hydration preceding or during the treatment was a risk factor,[18] as was the rate of IV infusions, with a slow infusion over an hour reported to halve renal impairment incidence as compared with a rapid bolus.[19] A recent study of 216 patients on Acyclovir for CNS infection reported that renal function varied according to the hydration volume.[20] The adverse events were also related to the high dose, which was required in patients with encephalitis as it was poorly water-soluble and had an oral bioavailability of 10–20%;[21] hence, intravenous administration was necessary.

The successful control of AKI brought on by Acyclovir depends on accurate diagnosis and efficient treatment. Due to

this, creatinine must be measured both before and often during the therapy (i.e. daily for at least the first 2–3 days). When receiving Acyclovir, the dosage should be changed if a patient develops renal failure. In addition, when dialysis is necessary, it should be started as soon as possible. Slow drug infusion over 1-2 hours, sufficient fluid replacement, and induction of high urinary flow rates (100-150 ml/h) should all be encouraged.

In obese patients, there is a need for dose adjustment for Acyclovir as the new data is emerging about antimicrobial dosing in obesity. The dose should be given based on adjusted body weight (AdjBW) instead of actual body weight (ABW), for which the height of the patient is required.[22]

The limitation of the study was that it was conducted at a single tertiary care hospital; multi-centered studies are required for generalisation of the results.

CONCLUSION

The study findings drew attention to the fact that Acyclovir can lead to AKI, and in some cases, it may also end up in dialysis. However, Acyclovir-induced AKI is a potentially preventable complication. Careful hydration with an adequate fluid balance and daily monitoring of renal functions are important for early renal impairment.

ETHICAL APPROVAL:
The study protocol was approved by the ethical committee of Liaquat National Hospital, Karachi (Ref: App# 0632-2021 LNH- ERC).

PATIENTS' CONSENT:
Written informed consent was obtained from all the patients participating in this study.

COMPETING INTEREST:
The authors reported no potential conflict of interest.

AUTHORS' CONTRIBUTION:
RB: Conceptualised the study, collect and analysed the data.
SNZ: Designed the study, critically reviewed and revised the draft.
RB, SNZ: Prepared the initial draft, read and approved the final manuscript.
All authors approved the final version of the manuscript.

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