

Delays in Initiation of Acyclovir Therapy in Herpes Simplex Encephalitis

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ABSTRACT: Background: Diagnosis of herpes simplex encephalitis (HSE) is based on clinical findings, MRI, and detection of herpes simplex virus (HSV) DNA in cerebrospinal fluid (CSF) using polymerase chain reaction amplification. Delays in starting treatment are associated with poorer clinical outcomes. We assessed the timing of initiation of acyclovir therapy in HSE. **Methods:** Inpatient databases from seven hospitals in Winnipeg, Manitoba were used to identify individuals diagnosed with encephalitis and HSE from 2004 to 2009. The time taken to initiate therapy with acyclovir and the reasons for delays were determined. **Results:** Seventy-seven patients were identified; 69 (90%) received acyclovir; in the others a non-HSV infection was strongly suspected. Thirteen patients were subsequently confirmed to have HSE. Acyclovir was initiated a median of 21 hours (3-407) after presentation in encephalitis cases, and a median of 11 hours (3-118) in HSE. The most common reason for delay was a failure to consider HSE in the differential diagnosis, despite suggestive clinical features. Where therapy was delayed in HSE patients, the decision to begin acyclovir was prompted by transfer of the patient to a different service (55%), recommendations by consultants (18%), imaging results (18%), and CSF pleocytosis (9%). **Conclusions:** Delays in initiating acyclovir for HSE are common, and are most often due to a failure to consider HSE in a timely fashion on presentation. In order to improve patient outcomes, physicians should be more vigilant for HSE, and begin acyclovir therapy expeditiously on the basis of clinical suspicion rather than waiting for confirmatory tests.

RÉSUMÉ: Retard à débiter le traitement par l'acyclovir dans l'encéphalite due au virus de l'herpès simplex. Contexte : Le diagnostic de l'encéphalite due au virus de l'herpès simplex (EHS) est fondé sur la clinique, l'IRM et la détection de l'ADN du virus de l'herpès simplex (VHS) dans le liquide céphalo-rachidien (LCR) au moyen de l'amplification en chaîne par polymérase. Si le traitement n'est pas commencé tôt, l'issue clinique en sera compromise. Nous avons examiné le moment du début du traitement par l'acyclovir dans l'EHS. **Méthode :** Nous avons identifié dans les bases de données de 7 hôpitaux de Winnipeg au Manitoba les individus chez qui un diagnostic d'encéphalite et d'EHS a été posé de 2004 à 2009. Nous avons déterminé le temps écoulé entre l'arrivée du patient et le moment où le traitement par l'acyclovir a été commencé et les raisons pour lesquelles l'administration de ce traitement avait tardé. **Résultats :** Soixante-dix-sept patients ont été identifiés; 69 d'entre eux (90%) ont reçu de l'acyclovir; chez les autres patients, une infection par un agent autre que le VHS était fortement soupçonnée. Chez 13 patients l'EHS a été confirmée par la suite. Le temps médian de début du traitement par l'acyclovir était de 21 heures (3 à 407 heures) après l'arrivée à l'hôpital chez les cas d'encéphalite et le temps médian était de 11 heures (3 à 118 heures) chez les cas d'EHS. La raison la plus fréquente du retard était le fait que l'EHS n'avait pas été prise en considération dans le diagnostic différentiel, malgré des caractéristiques cliniques suggestives de ce diagnostic chez le patient. Quand le traitement était retardé chez les patients atteints d'une EHS, la décision de commencer le traitement par l'acyclovir résultait du transfert du patient à un service différent (55%), la recommandation d'un consultant (18%), les résultats de l'imagerie (18%) et une pléiocytose du LCR (9%). **Conclusions :** Un retard à commencer le traitement par l'acyclovir dans l'EHS est fréquent et il est dû la plupart du temps au fait que ce diagnostic n'est pas envisagé en temps opportun, au moment où le patient arrive à l'hôpital. Les médecins devraient être plus vigilants afin d'améliorer le résultat chez le patient atteint d'une EHS et commencer le traitement par l'acyclovir le plus rapidement possible lorsque cette pathologie est soupçonnée au lieu d'attendre le résultats de tests confirmant ce diagnostic.

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Herpes simplex encephalitis (HSE) is a sporadic, necrotizing brain infection with an incidence of one to four cases per million people per year.¹ The clinical presentation typically includes fever, headache, and personality change, which may be accompanied by seizures, aphasia, and autonomic dysfunction.² Analysis of cerebrospinal fluid (CSF) usually reveals a moderate lymphocytic pleocytosis. A diagnosis of HSE can be confirmed with polymerase chain reaction (PCR) amplification of herpes simplex virus (HSV) DNA in CSF, but results are often not available quickly. Magnetic resonance imaging (MRI) of the brain also has a high degree of sensitivity and specificity, with characteristic lesions seen in the mesial temporal lobes and other limbic regions.³

Untreated HSE has a mortality rate of about 70 percent.⁴ Among survivors, more than 95 percent have residual neurological deficits.⁵ The advent of acyclovir in the 1980s offered substantial improvement in clinical outcomes.⁶ However, neurological morbidity remains high even in treated

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patients. Early initiation of acyclovir therapy offers the best chance of a good neurological outcome, with minimal risk.⁷⁻⁹ Delays in the diagnosis of HSE are commonplace, even after patients are admitted to hospital, because the differential diagnosis of encephalitis is broad. Results of confirmatory tests may not be immediately available, but intravenous acyclovir therapy can be initiated empirically on the basis of clinical suspicion alone.¹⁰

Guidelines issued by the Infectious Diseases Society of America (IDSA) recommend that all patients with suspected encephalitis should receive acyclovir, pending results of diagnostic studies.¹⁰ While studies have shown that treatment is often delayed in patients with suspected HSE, the reasons for this failure to start acyclovir promptly are less clear. We performed this retrospective study in order to determine how rapidly treatment is initiated in confirmed and suspected cases of HSE. We hypothesized that the administration of acyclovir is commonly delayed in the acute setting because emergency physicians and specialists tend to wait for the results of diagnostic tests, rather than expeditiously commencing empiric therapy.

METHODS

The study took place over a six-year period from 2004 to 2009 in Winnipeg, a Canadian city of population 750,000 with a referral base of about 1.2 million. An inpatient database of patients within the Winnipeg Regional Health Authority was used to identify adults admitted to the city's seven general hospitals with a diagnosis of either encephalitis or meningoencephalitis. For inclusion in the study, subjects were required to have a history of headache and fever, plus an alteration in level of consciousness and/or focal neurologic features. A subgroup of individuals with definite HSE was identified on the basis of confirmatory PCR results.

Where data were available, the time (in minutes) taken for the initial assessment to be performed by a physician after the patient's arrival at the emergency department was determined. Times were also recorded, to the nearest hour, for lumbar punctures and MRI scans, if these were performed. For each patient, it was determined whether intravenous acyclovir therapy was administered at any time during the hospital admission. In cases where acyclovir was given, the time that elapsed from arrival at the hospital to commencement of therapy was recorded, rounded to the nearest hour.

Among patients with HSE who did not receive acyclovir within six hours of arrival, the reasons for the delay were identified. Whenever possible, the factor that influenced the medical team to initiate acyclovir therapy later on (the treatment 'prompt') was identified.

RESULTS

Subjects

A total of 137 subjects were identified from the database. After excluding individuals who (i) were misclassified in the database (n=20), (ii) lacked encephalopathic or focal neurologic features (n=31), or (iii) had demonstrable bacterial or fungal infections (n=9), a cohort of 77 patients remained. The median age of the study population was 56 years (range 18-95), and 47

(61%) of the subjects were male. Of these, 13 (17%) had definite HSE confirmed by PCR assay (mostly HSV type 1), representing an annual incidence of 1.8 cases per million population. The remaining 64 individuals were classified as having non-HSV encephalitis. These patients comprised 44 (57%) who were PCR-negative, 7 (9%) in whom no PCR test was performed but in whom an alternate pathogen was identified, and 13 (17%) in whom no PCR test was performed and no infectious agent was found. In this final subgroup, HSE could not definitively be ruled out, but neither could it be diagnosed with any confidence.

Among patients diagnosed with viral encephalitides other than HSE, the most common pathogen identified was West Nile virus (n=15), followed by Epstein-Barr virus (3), varicella-zoster virus (2) and cytomegalovirus (1).

Time to Initial Assessment

Among the 13 patients with HSE, seven (54%) were seen within 45 minutes of arrival, and an additional two (for a total of 69%) were assessed within 90 minutes. For the remaining four (31%), precise times were not recorded.

CSF Findings

Among the patients diagnosed with definite HSE, the median time from arrival at hospital to lumbar puncture (LP) was seven hours (range 2-61). The CSF leukocyte count was elevated in all but one of the samples, with a median of 31 cells per microlitre (range 4-912). Among non-HSE patients, CSF leukocyte counts ranged from 0 to 686 cells per microlitre, with a median of 42.

MRI Findings

Among the 13 patients with definite HSE, ten (77%) underwent an MRI scan. All of the scans demonstrated lesions that were consistent with HSE. With one exception, the MRI scans were performed many hours (median 32; range 8-45) after acyclovir treatment had been started, and therefore the MRI findings did not play a role in the decision to start treatment. In only one case was acyclovir started immediately after the MRI results were obtained.

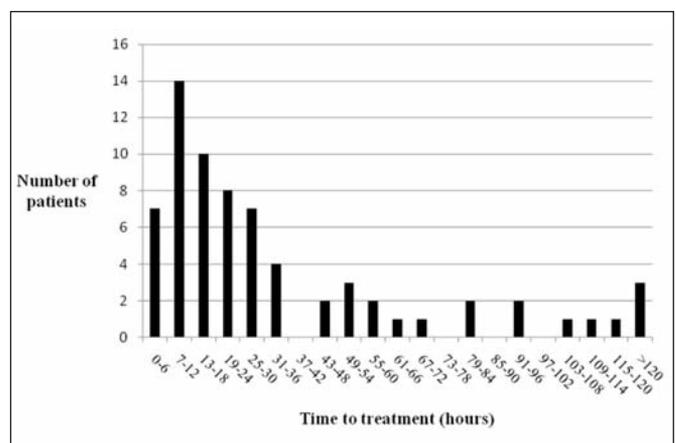


Figure 1: Time from arrival at hospital to initiation of the first dose of acyclovir in the 69 subjects with suspected or confirmed HSE.

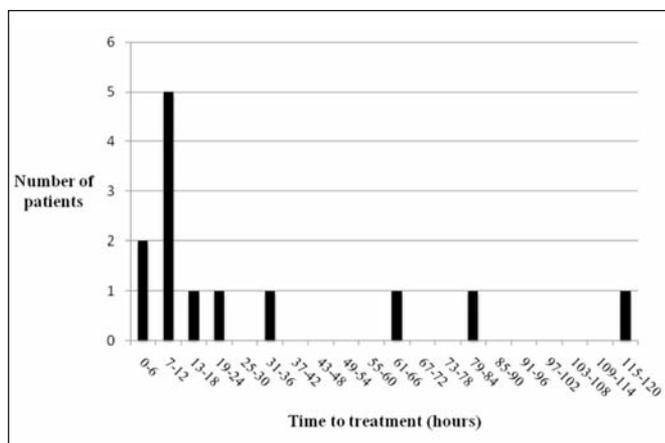


Figure 2: Time from arrival at hospital to initiation of the first dose of acyclovir in the 13 subjects with HSE.

Time to Treatment

Across the study population as a whole, 69 (90%) of the 77 patients received acyclovir. The time that elapsed between initial assessment and administration of the first dose of acyclovir was highly variable, ranging from 3 to 407 hours with a median of 21 hours (Figure 1). Among the 13 patients with confirmed HSE, all of whom received acyclovir, the time to the first dose was shorter, with a median of 11 hours and a range of 3 to 118 hours (Figure 2). Seven of the HSE patients (54%) received treatment within 12 hours of arrival at the hospital, and two (15%) within six hours. Two of the HSE patients died during their hospital admission, and their times to treatment were 11 and 118 hours.

One of the patients with HSE, who waited 84 hours for his first dose of antiviral medication, had initially been sent home from his local emergency department without treatment, despite a history of headache, fever, and confusion. He returned three days later with a worsening of his symptoms, at which time a computed tomogram (CT) scan revealed signal change in his right temporal lobe. A suspicion of HSE was not raised until he was transferred to the intensive care unit 12 hours later, at which time he was started on intravenous acyclovir.

Reasons for Treatment Delay

In 10 (85%) of the 13 patients who had HSE, acyclovir was not started until after the preliminary results of the CSF analysis were available (Table 1). This indicates that preliminary CSF results played a key role in the decision to initiate antiviral therapy – even if this connection was not explicitly documented.

Among the 11 patients with HSE who waited more than six hours to be treated, the most common reason for the delay was a failure to consider HSE among the initial diagnostic possibilities (Table 2). In three cases, the patients were presumed to have bacterial or viral meningitis, and a urinary tract infection was suspected in another two. For two of the patients, no specific diagnosis was documented. In the remaining four cases, HSE was considered in the differential diagnosis, but acyclovir therapy was not initiated.

Table 1: Timing of first acyclovir dose relative to lumbar puncture in patients with confirmed HSE

Time of first acyclovir dose	Number of patients
>4 hours before LP	1
2-4 hours before LP	0
1 hour before LP	0
Same time as LP	2
1 hour after LP	3
2-4 hours after LP	1
>4 hours after LP	6
Total	13

Reasons for Starting Therapy

Among the 11 ‘delayed treatment’ patients, a variety of factors were identified that prompted the treating physician to begin acyclovir (Table 3). In six (55%) of the 11 cases, treatment was started soon after the patient was signed over to a new medical team – either an internal medicine service, an intensive care unit, or a different hospital altogether. The next most common treatment prompt, in two patients (18%), was advice from an infectious diseases specialist. Another two were treated on the basis of an abnormal CT or MRI scan. In one case the chart indicated that treatment had been started on the basis of CSF pleocytosis, although CSF abnormalities were probably influential in other cases as well. Among the 13 HSE patients, the only individual in whom treatment was begun on the basis of MRI abnormalities was also the only patient to have a normal CSF cell count. This individual also waited the longest for treatment to be started (118 hours).

Table 2: Acute management in patients with confirmed HSE

Initial management	Number of patients at 6 hours	Number of patients at 12 hours
Viral encephalitis not considered	7	4
Viral encephalitis considered; acyclovir not given	4	2
Acyclovir given	2	7
Total	13	13

Table 3: Reasons for initiating treatment in cases in which acyclovir therapy was delayed in patients with confirmed HSE

Reason for Starting Treatment	Number of cases
Transfer to a different hospital or service	6
Infectious diseases consultation	2
CT or MRI results	2
CSF pleocytosis	1
Total	11

DISCUSSION

We have shown that a cohort of patients presenting acutely at emergency departments with suspected HSE received their first dose of acyclovir a median of 21 hours after arrival, whereas the median time for cases with confirmed HSE was 11 hours. This difference probably reflects a greater degree of confidence in the clinical diagnosis. In the HSE group, all but two (11/13 or 85%) received acyclovir therapy outside a six-hour time window. Of these 11 individuals, seven were not initially suspected of having HSE. The remaining four were identified as possible HSE cases, but antiviral therapy was nevertheless delayed. The most common reason for delaying treatment was failure to consider HSE in the differential diagnosis. In cases where treatment was started late, this commonly took place after care of the patient had been transferred to a different medical team.

Although we cannot know the precise impact of treatment delays on our study population, it is well known that delayed initiation of therapy is associated with increased morbidity and mortality in HSE, and that longer delays are associated with more serious neurological consequences.⁹ A study carried out in a large public hospital in Los Angeles¹¹ revealed a median time of 11.8 hours to initiation of acyclovir therapy (n=24) among patients with suspected HSE, compared with 21 hours in the present study (n=69) and 11 hours in the HSE subgroup (n=13). However, 71% of the patients in the Los Angeles study¹¹ did not receive acyclovir in the emergency room, but instead waited until they had been transferred to an inpatient ward, where they came under the care of another service. In our study, transfer to a different hospital or service was the impetus for initiating acyclovir in 6/11 (55%) of the HSE patients.

Raschilas et al⁸ found that the mean delay between hospital admission and initiation of acyclovir therapy among 93 patients with HSE in France was two days, and that a delay of two or more days in starting acyclovir therapy was significantly associated with death or serious disability. A separate study of 184 HSE patients in France by Poissy et al¹², which measured times in intervals of days, showed that the median delay was one day. A recent report from a United Kingdom teaching hospital showed that the median time from presentation to starting

acyclovir was 48 hours (2-432 hours) in 21 cases of suspected HSE cases, with only a single confirmed case of HSE.¹³ Delays in obtaining CT scans prior to lumbar puncture were thought to be partly responsible. In a study of 42 patients with HSE in New Zealand, McGrath et al⁹ reported that only 15/42 (36%) of patients presenting with HSE received their first infusion of acyclovir on the day of admission. Furthermore, they found that "good outcome" patients had waited an average of 1.8 days from the time of admission to receive their first dose of intravenous acyclovir, whereas "poor outcome" patients had waited 4.0 days (p<0.025).⁹ Thus, although the treatment delays experienced by the HSE patients in our study are considerable, they are shorter than those documented in most previous reports.

Our analysis supports the observation that there is a tendency not to begin treatment until the results of an LP are available.⁹ Only 3/13 (23%) patients with HSE were started on acyclovir before the CSF analysis was available, even though all 13 had a clinical picture that was suggestive of HSE. Although an LP needs to be performed as soon as safely possible on patients with suspected encephalitis, it is not a prerequisite for starting treatment. Nor does the administration of acyclovir compromise the diagnostic value of the LP, provided that the CSF is obtained within five days of starting treatment.¹

Furthermore, our results suggest that physicians may interpret a normal CSF cell count as excluding HSE. Among our 13 patients with definite HSE, the individual who waited longest for treatment to be started (118 hours) was also the sole patient to have a normal CSF leukocyte count. For this individual, treatment was not started until the fifth day of admission, after an MRI scan revealed lesions characteristic of HSE. Soon afterwards, the confirmatory PCR test was reported to be positive; however, the patient died a few days later. A French study¹² provides further evidence that a normal CSF cell count can lead to a delayed diagnosis of HSE. It examined risk factors contributing to treatment delay (defined as more than 24 hours), and found that patients with a low or normal CSF cell count (<10 leukocytes per microlitre) were 2.5 times more likely to experience late treatment.

This study has two principal limitations. Firstly, the nature of the study, namely a retrospective review of patient records, meant that our analysis was constrained by the quality of data contained in the hospital charts. In particular, documentation of the history and physical examination was often incomplete. It was possible to determine that the patient presented with fever, headache and altered mentation, but the details were often lacking beyond this basic information. Similarly, the exact times at which investigations and treatments were initiated were frequently not recorded. The factors influencing the initiation of acyclovir therapy were not always clearly indicated. Secondly, it is possible that some of the patients classified as non-HSE were incorrectly assigned, because in 13 cases a confirmatory PCR test for HSV DNA was never performed.

Physicians in acute care facilities commonly fail to consider HSE when assessing patients who have clinical features typical of the disease. As a consequence, antiviral treatment is frequently delayed. The impact on morbidity and mortality is likely to be significant. A greater awareness of this disease among emergency physicians and their colleagues would likely lead to earlier treatment and better clinical outcomes.

In patients with bacterial meningitis, it is known that delays in initiating antibiotics can adversely affect morbidity and mortality.¹⁴⁻¹⁷ It is generally recommended that antibiotics be administered empirically, and not withheld while the results of brain imaging or CSF analysis are pending. We suggest that a similar approach be adopted in suspected HSE, with the first dose of intravenous acyclovir initiated as soon as the possibility of HSE is seriously considered, rather than waiting until the results of preliminary investigations are available. If HSE is still seriously considered after another eight hours have elapsed, then subsequent doses may be administered. This change in the use of empirical therapy for suspected HSE would likely result in improved outcomes for patients suffering from this devastating disease.

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