

# An unexpectedly high occurrence of aciclovir-induced neuropsychiatric symptoms in patients treated for herpesvirus CNS infection: a prospective observational study

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Received 30 April 2019; returned 12 June 2019; revised 13 July 2019; accepted 16 July 2019

**Background:** Aciclovir is effective in herpesvirus infections of the CNS. Aciclovir-induced neuropsychiatric symptoms (AINS) have been reported and are associated with high CSF concentrations of aciclovir metabolite 9-carboxymethoxymethylguanine (CMMG). Risk factors except for renal failure have not been explored, and disruption of the blood–brain barrier (BBB) in acute CNS infection may be of interest.

**Objectives:** To investigate the impact of risk factors on aciclovir and CMMG concentrations, and to relate the results to AINS.

**Methods:** We investigated 21 consecutively included, consenting patients treated with aciclovir or valaciclovir for herpesvirus CNS infection. Regression models were constructed to study the impact of risk factors including BBB disruption, as measured with CSF:serum albumin ratio, on CSF aciclovir and CMMG concentrations. Medical records were assessed retrospectively to identify patients with AINS.

**Results:** Increased CSF:serum albumin ratio, as well as decreased renal function and high aciclovir doses, was associated with increased aciclovir and CMMG concentrations in the CSF. We identified five patients with new neuropsychiatric symptoms; four of those were considered to have AINS and had increased CSF CMMG concentrations. Only one patient without suspicion of AINS had an increased CSF CMMG concentration.

**Conclusions:** In patients with herpesvirus CNS infections, BBB disruption is associated with increasing aciclovir and CMMG CSF concentrations. We also found an unexpectedly high number of patients with AINS. Evaluation of CSF:serum albumin ratios, renal function and CSF concentrations of aciclovir and CMMG may all contribute to the optimization of aciclovir dosing and avoidance of AINS.

## Introduction

Aciclovir is the first-line treatment for patients with infections of the CNS caused by herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2) and varicella-zoster virus (VZV).<sup>1</sup> The efficacy of treatment has only been studied in herpes simplex encephalitis (HSE). Intravenous (iv) aciclovir at 10 mg/kg q8h has in randomized trials been shown to decrease mortality in HSE markedly,<sup>2,3</sup> but still the disease is associated with considerable morbidity.<sup>4</sup>

With the substantial morbidity taken into account, higher dosages than those used in studies on efficacy are sometimes

considered in young patients with HSE without renal impairment, although studied retrospectively.<sup>5</sup> Furthermore, several national guidelines and international expertise recommend treatment of VZV encephalitis with iv aciclovir at 10–15 mg/kg q8h,<sup>1,6</sup> since VZV is less susceptible to aciclovir.<sup>7</sup> However, the relationship between aciclovir concentrations, viral *in vitro* susceptibility and clinical efficacy is uncertain at best. Research on dosing and duration of aciclovir treatment is scarce, and increasing dosages may have negative consequences.

Aciclovir has the well-known and prevalent adverse effect of causing reversible nephrotoxicity, which can be prevented by

adequate hydration and reducing the dosage.<sup>8</sup> Less noticed is neurotoxicity related to aciclovir, aciclovir-induced neuropsychiatric symptoms (AINS), first reported in the 1980s.<sup>9</sup> The AINS incidence in Sweden has been estimated to be at least one AINS case per million inhabitants, when retrospectively studied.<sup>10</sup> A multitude of symptoms have been described, including confusion, hallucinations, ataxia, involuntary movements, somnolence and coma, mainly in patients with acute or chronic renal failure.<sup>11</sup> However, symptoms occurring in HSE may be difficult to distinguish from AINS, and to date no systematic approach or scoring system to separate them has been published.

The association between AINS and aciclovir concentrations is not fully understood.<sup>12</sup> Approximately 90% of aciclovir is excreted unchanged in the urine in patients with normal kidney function. The remaining part is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to the inactive main metabolite 9-carboxymethoxymethylguanine (CMMG). As renal function declines, metabolism to CMMG makes an increasing contribution to total clearance.<sup>13</sup> More recent studies have shown an association between AINS and increased serum and CSF concentrations of CMMG in a more consistent manner compared with aciclovir concentrations,<sup>11,13</sup> and as a result CMMG has been proposed as a more reliable marker of AINS than aciclovir.

Besides decreased renal function, there may be other factors influencing CSF concentrations of aciclovir and CMMG. A few studies on CSF concentrations of aciclovir have been published, showing relatively stable aciclovir concentrations in CSF compared with serum, and lower AUC in CSF compared with serum,<sup>14–16</sup> suggesting slow diffusion into and active transport out of CSF, substantiating the importance of the integrity of the blood–brain barrier (BBB) for aciclovir penetration to the CSF/CNS compartment. A damaged BBB, such as might occur in acute CNS infection, allows increased passage of molecules, usually accompanied by a decrease in functions of efflux mechanisms.<sup>17</sup> Increased drug penetration due to BBB damage in CNS infections has been observed in studies of anti-retrovirals<sup>18</sup> and antibiotics.<sup>19,20</sup> However, studies during aciclovir treatment are lacking.

Our primary aim was to investigate the impact of different risk factors, including disruption of the BBB, on the concentrations of aciclovir and CMMG in patients treated for CNS infections. Our secondary aim was to relate our findings, including CMMG concentrations, to neuropsychiatric symptoms.

## Patients and methods

### Patients

Patients ( $\geq 18$  years of age) with suspected or confirmed herpes virus infection of the CNS, treated with iv aciclovir or oral valaciclovir, were consecutively enrolled in the study between 9 September 2013 and 20 January 2016 at the Department of Infectious Diseases at Sahlgrenska University Hospital, Gothenburg, Sweden. The Medical Ethics Committee at Gothenburg University approved the study (Dnr 407-13), and informed consent was obtained.

### Sampling and analysis of serum and CSF

Pairs of serum and CSF were obtained on one or multiple occasions from each patient. The samples were obtained on days 1–2, 3–5, 6–9, 10–14, 15–21 and 22–30 after initiation of aciclovir treatment. Lag time between dose

administration and sampling was not determined in advance, to enable analysis of the pharmacokinetic profile at group level in a scenario that mimics the clinical setting. CSF and blood samples were coded and stored at  $-70^{\circ}\text{C}$  until further analysis.

Estimation of renal function was determined from analysis of serum creatinine and serum cystatin C.  $\text{CL}_{\text{CR}}$  was calculated using the Cockcroft–Gault formula,<sup>21</sup> and glomerular filtration rate (GFR) based on cystatin C was calculated using the CAPA (Caucasian, Asian, paediatric and adult) formula.<sup>22</sup> Development of acute kidney injury was further classified according to RIFLE (risk, injury, failure, loss of function, end-stage renal disease) criteria.<sup>23</sup>

Albumin levels in CSF and serum were measured by immunonephelometry on a Beckman image immunochemistry system (Beckman Instruments, Beckman Coulter, Brea, CA, USA). The albumin ratio was calculated [CSF albumin (mg/L)/serum albumin (g/L)] and used as an indicator of the integrity of the BBB,<sup>24</sup> with normal upper limits of  $6.8 \times 10^{-3}$  for patients  $\leq 45$  years of age and  $10.2 \times 10^{-3}$  for patients  $> 45$  years of age,<sup>25</sup> similar to the categorization suggested by Reiber and Felgenhauer.<sup>26</sup> For ease of interpretation, albumin CSF:serum ratio is presented without adding the magnitude indicator of  $\times 10^{-3}$  in the following sections.

The aciclovir and CMMG concentrations were determined at the Department of Clinical Pharmacology, Karolinska University Hospital, Huddinge, Stockholm, Sweden, using solid-phase extraction followed by HPLC with fluorescence detection. The limit of detection and the limit of quantification were  $0.15 \mu\text{mol/L}$ . CMMG concentrations lower than the limit of detection of  $0.15 \mu\text{mol/L}$  were assigned the value of  $0.08 \mu\text{mol/L}$  for visualization purposes.

### Assessments of the risk of developing neuropsychiatric symptoms

We retrospectively studied the medical records of all included patients for neuropsychiatric symptoms previously associated with AINS, specifically generalized neuropsychiatric symptoms such as confusion, hallucinations, ataxia, involuntary movements, somnolence and coma.<sup>11</sup> The study protocol did not include specific instructions on documentation, but documentation had been made on a daily basis according to standard procedure. Fever, headache and focal CNS symptoms, more typical of viral CNS infection, were considered unlikely to be associated with treatment.<sup>27</sup> To further distinguish AINS from symptoms of viral CNS infection, symptoms needed to have developed during aciclovir treatment, and resolved at dose reduction or end of treatment. In addition, concomitant medications or pathologies needed to be ruled out as responsible for such symptoms. The risk assessment also included data on aciclovir doses and changes in serum creatinine, as decreased renal function has been previously associated with AINS. The assessments were performed blinded without knowledge of the aciclovir or CMMG concentrations by three of the authors: an experienced neurologist (J. Lycke) and two clinicians at the Department of Infectious Diseases (M. S., J. Lindström). The patient was considered to have suspected AINS if two or three of the raters were in agreement.

### Statistical analysis and subgrouping

Multivariable regression models were constructed to study the impact of relevant independent variables on the studied dependent variables. The SAS procedure mixed was used, considering that some of the patients were sampled at more than one timepoint, using the autoregressive covariance pattern that was found optimal based on the lowest Akaike information criterion. The residual plots were reviewed for assumption of normal distribution. Standard errors and 95% CIs were estimated based on robust sandwich estimators in order to adjust for residuals' potential deviation from a normal distribution. The mixed models were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Group comparisons were performed with the Mann–Whitney *U*-test, using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). All tests were two-tailed and conducted at the 0.05 significance level.

## Results

During the 29 month period of 2013–16, 21 patients were enrolled in the study. Overall, 34 CSF samples and 32 serum samples were obtained from the 21 patients. Patient data and characteristics are presented in Table 1. As treatment duration and timing of inclusion differed, the number of samplings for each patient varied from one to three. Owing to the study being performed at a referral clinic, all but one patient had their primary diagnostic CSF sampling made before inclusion in the study.

### Risk factors and CSF concentrations of aciclovir and CMMG

Median aciclovir concentration in serum was 14.5  $\mu\text{mol/L}$  (range 2.7–120) and in CSF 8.7  $\mu\text{mol/L}$  (3.1–40). Median CMMG concentration measured in serum was 2.5  $\mu\text{mol/L}$  (range 0.29–57) and in CSF 0.18  $\mu\text{mol/L}$  (<0.15–6.4) (Figure 1).

In our multiple linear regression model, significant associations were made between several independent risk factors and concentrations of aciclovir and CMMG in the CSF (Table 2).

#### BBB integrity

An increase of 10 in CSF:serum albumin ratio was associated with a mean increase in CSF aciclovir concentration of 1.50  $\mu\text{mol/L}$  (95% CI 1.29–1.71,  $P<0.001$ ) (Figure 2a) and a mean increase in CMMG CSF concentration of 0.39  $\mu\text{mol/L}$  (95% CI 0.36–0.42,  $P<0.001$ ) (Figure 3a).

#### Renal insufficiency

A decrease in  $\text{CL}_{\text{CR}}$  of 10 mL/min was associated with a mean increase in CSF aciclovir concentration of 1.43  $\mu\text{mol/L}$  (95% CI 0.76–2.10,  $P=0.015$ ) (Figure 2b) and a mean increase in CMMG CSF concentration of 0.16  $\mu\text{mol/L}$  (95% CI 0.08–0.25,  $P=0.0027$ ) (Figure 3b).

#### Aciclovir dosing

An increase in aciclovir dose of 1 mg/kg was associated with a mean increase in CSF aciclovir concentration of 1.70  $\mu\text{mol/L}$  (95% CI 1.22–2.19,  $P<0.001$ ) (Figure 2c) and a mean increase in CMMG CSF concentration of 0.09  $\mu\text{mol/L}$  (95% CI 0.02–0.16,  $P=0.017$ ) (Figure 3c).

#### Lag time

CSF aciclovir concentration decreased by a mean of 0.78  $\mu\text{mol/L}$  (95% CI 0.21–1.35,  $P=0.015$ ) for every hour that passed between dose administration and sampling, and CSF CMMG concentrations decreased by 0.05  $\mu\text{mol/L}$  (95% CI 0.02–0.07,  $P=0.0038$ ).

#### Weight

A 10 kg increase in weight was associated with a mean increase in CSF aciclovir concentration of 2.00  $\mu\text{mol/L}$  (95% CI 1.00–2.19,  $P=0.0005$ ) and a mean increase in CSF CMMG concentration of 0.22  $\mu\text{mol/L}$  (95% CI 0.05–0.39,  $P=0.013$ ).

#### Age and gender

Neither age nor gender was significantly associated with changes in CSF aciclovir or CMMG concentrations.

### Neuropsychiatric symptoms

Five out of 21 patients were identified with neuropsychiatric symptoms that developed after initiation of aciclovir treatment and subsided after a dose decrease or after the end of treatment (Table 1; see also the short descriptive case series available as [Supplementary data](#) at JAC Online). Four of the patients (Patients 4, 6, 7 and 19) deteriorated during treatment, with increased confusion, while one patient (Patient 20) presented with decreased muscle tonus and anxiety, not previously associated with AINS. None of the included patients was suspected to have AINS by the treating clinicians. Looking at expected risk factors, five out of five identified patients had decreased renal function, four out of five were treated with an aciclovir dose  $>10$  mg/kg q8h and four out of five had indication of BBB damage with elevated CSF:serum albumin ratio (Table 1).

Excluding Patient 20, who did not present a picture similar to earlier published cases, patients assessed with neuropsychiatric symptoms had higher peak CMMG concentrations in any CSF sample ( $n=4$ ; median 2.15  $\mu\text{mol/L}$ ; range 0.68–6.4) compared with patients without typical neuropsychiatric symptoms ( $n=17$ ; <0.15  $\mu\text{mol/L}$ ; <0.15–0.77) ( $P=0.0003$ ) (Figure 4). Only one patient (Patient 11) had a CMMG concentration in CSF  $>0.5$   $\mu\text{mol/L}$  without recorded symptoms indicating AINS, and although this patient had BBB damage, he had a standard aciclovir dose of 10 mg/kg q8h and normal renal function. Peak serum CMMG concentration was also significantly higher in patients with AINS ( $n=4$ ; median 23.85  $\mu\text{mol/L}$ ; range 5.2–57.0) compared with patients without typical neuropsychiatric symptoms ( $n=15$ ; 1.7  $\mu\text{mol/L}$ ; 0.74–12.0) ( $P=0.0093$ ).

## Discussion

In this study, we show that damage to the BBB has a significant impact on aciclovir and CMMG pharmacokinetics in a clinical setting. We also reinforce the association between increased concentrations of CMMG in the CSF and neuropsychiatric symptoms, which were surprisingly prevalent.

Looking at the results from our regression models, our findings demonstrate that damage to the BBB in the acute phase of CNS infection is associated with increased penetration of aciclovir and CMMG into the CNS/CSF compartment. The association was proportionally more pronounced when looking at CMMG compared with aciclovir, suggesting a larger impact of BBB damage on CMMG CNS pharmacokinetics, possibly owing to it being more difficult for CMMG to cross the BBB compared with aciclovir, consistent with pharmacokinetic data reported by Smith *et al.*<sup>16</sup> The same study also describes that CMMG concentrations in the CSF do not vary considerably over time when in steady-state. This is not fully supported in our material since there is a change in CMMG concentration in relation to lag time from dose administration to sampling. However, the change is very small whereas the change in the aciclovir counterpart is more dynamic. Both CMMG and aciclovir concentrations were in some cases higher in CSF compared with serum, suggesting accumulation, and slow clearance out of the

**Table 1.** Characteristics of included patients, their treatment and CSF concentrations of aciclovir (ACV) and CMMG at all sampling timepoints

Patient	Age (years)	Gender	Weight (kg)	Indication for treatment	ACV dose q8h (mg/kg)	Lag time from dose to sampling (h)	Treatment duration (days)	Estimated CL <sub>CR</sub> (mL/min)	Serum concentration (µmol/L)			CSF concentration (µmol/L)			Neuropsychiatric symptoms during treatment
									ACV	CMMG	RIFLE	ACV	CMMG	ACV	
1 <sup>a</sup>	70	M	56	herpes encephalitis	10	7.5	13	80	R	5.7	0.74	8.4	0.15	N/A	
1 <sup>b</sup>	10				10	9	20	71		2.7	0.29	7.1	<0.15	15.4	
1 <sup>c</sup>	10				10	8.5	27	57		5	0.59	8.5	<0.15	11.7	
2	79	F	52	herpes encephalitis	11	6.5	9	61	R	70	12	11	0.27	7	
3	66	M	89	suspected varicella meningitis	1000 <sup>d</sup>	1	14	84	F	29	1.7	3.1	<0.15	6.9	
4 <sup>a</sup>	35	M	98	herpes encephalitis	15	6	2	30	F	110	57	40	3.3	29.4	confusion, improved at dose adjustment
4 <sup>b</sup>	4				12	7.5	9	125		25	2.8	7.5	0.15	15.7	
4 <sup>c</sup>	4				12	8	16	149		10	1.5	10	0.19	23.8	
5	30	M	100	suspected encephalitis	10	6	3	109		9.6	1.3	6.7	<0.15	24.3	
6 <sup>a</sup>	64	F	60	herpes encephalitis	12	3.5	3	40	R	50	9.7	24	0.68	20.1	confusion, improved at end of treatment
6 <sup>b</sup>	12				12	4	13	65		18.6	2.7	14	0.3	15.4	
6 <sup>c</sup>	12				12	8	21	70		11	2.3	12	0.23	11.9	
7 <sup>a</sup>	65	M	76	recurrent herpes encephalitis	15	2.5	8	109	I	55	18	16	0.29	14.7	confusion, improved at end of treatment
7 <sup>b</sup>	15				15	4.5	15	51		120	38	29	1	10.5	
7 <sup>c</sup>	15				15	21	29	35		11	11	8.2	0.66	14.6	
8	55	M	77	herpes encephalitis	10	5.5	13	122		11	1	6.7	<0.15	7.4	
9 <sup>a</sup>	58	M	68	stroke	11	1	5	56		75	10	12	0.27	9.3	
9 <sup>b</sup>	10				10	6.5	11	52		20	5	11	0.26	11.7	
10	40	M	120	herpes meningoencephalitis	10	1	12	184		13	0.9	8.5	<0.15	9.6	
11	41	F	67	herpes meningitis	10	4.5	7	117		14	1.5	17	0.77	26.7	
12	67	M	78	suspected encephalitis	9	1.5	5	87		31	4.9	8.9	0.17	13.8	
13	26	F	50	suspected encephalitis	15	8	3	119		6.1	1.2	5.9	<0.15	8.6	
14	58	M	87	herpes meningitis	1000 <sup>d</sup>	1	10 <sup>e</sup>	115		13	2	4.8	<0.15	8.6	
15 <sup>a</sup>	65	F	67	herpes encephalitis	9	6	6	73		10	2.3	7.7	0.16	8.5	
15 <sup>b</sup>	16				9	3	11	79		40	5.4	7.6	<0.15	8.8	
16	39	F	77	herpes encephalitis	14	1	13	131		N/A	N/A	8	<0.15	22.5	
17	49	F	72	herpes meningitis	9	1.5	3	129		17	1.6	7.5	<0.15	4.1	
18	53	M	85	varicella meningitis	14	5.5	2	123		N/A	N/A	14	0.24	13.3	
19 <sup>a</sup>	75	F	57	varicella encephalitis	10	7	7	54	R <sup>f</sup>	15	5.2	28	6.4	162.4	confusion, improved at end of treatment
19 <sup>b</sup>	10				10	7	14	68		13	3.6	27	3.8	108.1	
20 <sup>a</sup>	55	F	68	Ramsay Hunt syndrome	14	2.5	2	131	F	31	3.8	6.5	<0.15	1.7	anxiety, improved slowly at end of treatment
20 <sup>b</sup>	5				5	3	9	60		12	3	3.3	<0.15	1.4	
21 <sup>a</sup>	38	M	81	varicella encephalitis	14	4.5	1	141		9.9	1.1	12	0.2	28.8	
21 <sup>b</sup>	14				14	2.5	3	135		19	1.9	14	0.24	18	

ACV dose, mg iv aciclovir per kg body weight in a single dose, administered three times daily, except in patient 20<sup>b</sup>, where doses were administered twice daily; N/A, not available; M, male; F, female; (RIFLE column) R, risk; I, injury; F, failure; shaded areas indicate patients assessed to have AINS.

<sup>a</sup>First sampling in patient where repeated sampling was performed.

<sup>b</sup>Second sampling.

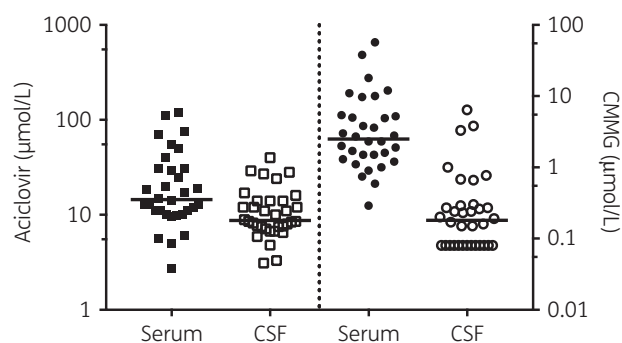
<sup>c</sup>Third sampling.

<sup>d</sup>Treatment with oral valaciclovir in single dose (mg), three times daily.

<sup>e</sup>Patient had previously received valaciclovir in a lower dose regimen as prophylaxis.

<sup>f</sup>Patient did not fulfil RIFLE criteria based on creatinine, but calculation of GFR according to cystatin C CAPA estimated GFR at 30 mL/min, corresponding to at least risk of acute kidney failure.





**Figure 1.** Distribution of aciclovir (left of divider) and CMMG (right of divider) in serum ( $n=32$ ) and CSF ( $n=34$ ) samples from patients ( $n=21$ ) treated with aciclovir for herpesvirus CNS infection. Limit of detection is 0.15; values  $<0.15$  are set to 0.08 for visualization purposes. Bar is set at median.

CNS for both molecules. In addition to BBB damage, and according to expectations, changes in  $CL_{CR}$  had an impact on aciclovir and CMMG concentrations, as did increasing aciclovir doses. Notably, increased age was not associated with increased concentrations, possibly as an effect of decreased renal function already being considered in our models. Increased weight, on the other hand, was associated with increased concentrations, suggesting that dosing based on weight may be suboptimal. Patients that weigh more will receive larger doses of aciclovir, while the increase in weight is not necessarily reflected in an increase in renal elimination, resulting in a higher risk of aciclovir and CMMG accumulation. We found concentrations of CMMG in CSF  $>0.5 \mu\text{mol/L}$ , previously associated with toxicity,<sup>13</sup> in 5/21 patients.

In our retrospective assessment, we were able to identify a surprisingly high number of patients with symptoms consistent with AINS, without taking aciclovir and CMMG concentrations into consideration. Although we identified five patients with neuropsychiatric symptoms, Patient 20 had anxiety as the main finding, a symptom that has not previously been described as typical of AINS. In addition, she did not have increased CMMG in the CSF samples, and we conclude that it is improbable that her anxiety was related to aciclovir treatment. Only in one patient with a CMMG level  $>0.5 \mu\text{mol/L}$  (Patient 11) were no neuropsychiatric symptoms found. However, it is possible that the patient may have had symptoms that were not noted in the medical records. Prospective, repeated assessments of neurological and psychiatric symptoms according to a protocol may have decreased the risk of missing such symptoms, but with the risk of impacting therapeutic decisions in this otherwise observational study.

An alternative explanation to impaired neurocognitive recovery could be autoimmune encephalitis. Recovery after cessation of aciclovir treatment, in combination with absence of anti-N-methyl-D-aspartate-receptor IgG antibodies in CSF and serum from the last sampling during admittance (data not shown), makes this highly unlikely. Autoimmune encephalitis is described as a later complication, with autoantibodies detected at 3 months after onset of HSE.<sup>28</sup>

Considering the invasiveness of CSF sampling, analysis of serum CMMG concentrations could be considered an attractive

alternative if proven reliable. Although the patients with AINS had higher median peak serum concentrations of CMMG, there was an overlap between groups, and two out of four patients with suspected AINS had serum CMMG concentrations  $<10.8 \mu\text{mol/L}$ , previously associated with AINS.<sup>11</sup> However, if CSF sampling is contraindicated, analysis of serum CMMG and aciclovir concentrations may still provide an indication of potentially harmful dosages if concentrations are high.

AINS has in most cases previously been associated with chronic renal failure, which none of our patients with elevated CMMG had in their medical history. However, Patients 4, 6 and 7 could be classified with acute kidney injury according to RIFLE criteria, and Patient 19 had decreased GFR according to calculation based on cystatin C. Only Patient 11 had increased CSF CMMG without any indication of kidney injury, and considering he was not suspected to have AINS, it is possible that renal function may be related to AINS in some respect that is not yet fully understood. While high concentrations of aciclovir in the CSF have been associated with AINS, there are conflicting reports,<sup>12</sup> and although CMMG has proven to be more reliable,<sup>13</sup> it is unknown how it relates to the pathogenesis.

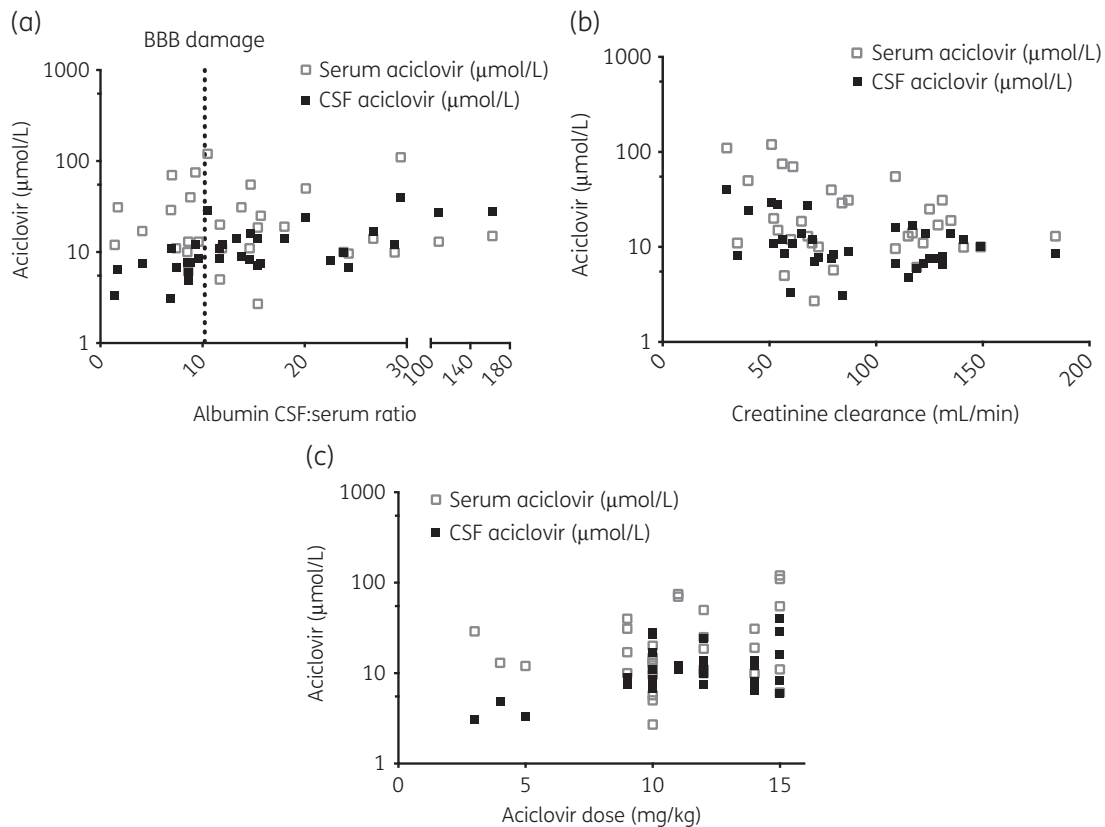
It is notable that none of the included patients was suspected to have AINS by the treating clinicians, highlighting the diagnostic difficulties and the need for additional diagnostic tools. Even though our assessment was retrospective, the patients were consecutively included, with a lower risk of selection bias when analysing CMMG compared with the previous studies.<sup>11,13</sup> Considering the consistency in our study between neuropsychiatric symptoms and increased CMMG concentrations, we can assert that analysis of CMMG in the CSF may be a useful tool when considering aciclovir-induced neuropsychiatric toxicity, especially since a systematic approach is otherwise lacking.

Although pharmacokinetic changes associated with BBB damage may be detrimental with regard to AINS, there may be positive effects associated with increased CNS penetration of aciclovir. Since BBB damage is most pronounced in the early stages of herpesvirus CNS infections, when viral replication is thought to play an important role in the pathogenesis,<sup>29</sup> increased concentrations of aciclovir in the CSF might potentially be beneficial, similar to the rationale for consideration of increased aciclovir dosages in selected patients. In the retrospective study on patients with HSE by Stahl *et al.*<sup>5</sup> where dosages of aciclovir were compared, a dosage of 15 mg/kg q8h did not increase the efficacy of treatment over a dosage of 10 mg/kg q8h, measured by looking at poor versus favourable outcome after treatment. Considering the increase in aciclovir concentrations in patients with BBB damage, a possible explanation for the lack of efficacy of increased dosages is that the increased dosages may be excessive. Although there is very little previous data on the penetration of aciclovir into the CNS in regard to BBB damage, a correlation between the albumin CSF:serum ratio and aciclovir CSF concentrations has previously been shown by Pouplin *et al.*<sup>30</sup> in six patients treated with valaciclovir for HSE. In this context, it is proposed that BBB damage may have an impact on the feasibility of oral treatment of HSE, but, as discussed by Bodilsen *et al.*,<sup>31</sup> drawing conclusions on efficacy based on aciclovir CSF concentrations is hazardous.

Although AINS seem to be reversible, they are detrimental to the patient and may obscure the symptomatic progress of the treated

**Table 2.** Multiple linear regression models for aciclovir and CMMG CSF concentrations in 21 patients treated with aciclovir for CNS infection (34 samples)

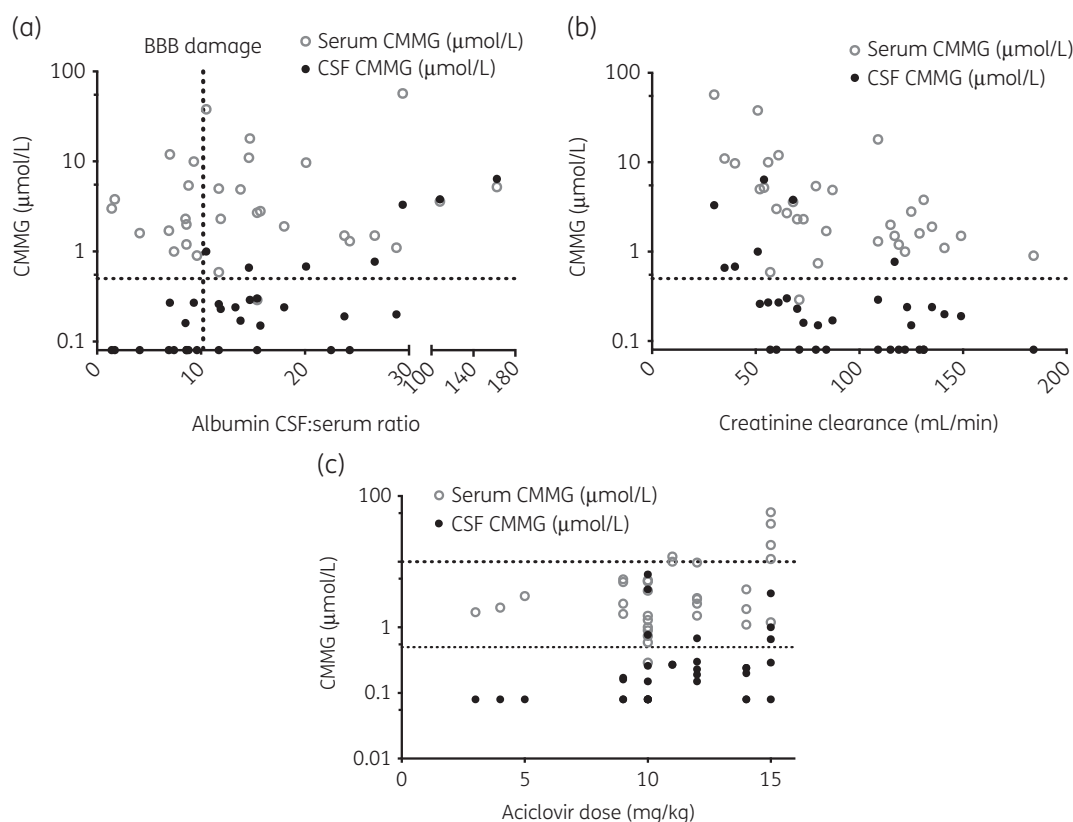
Independent variable	Comparison	Aciclovir CSF concentration		CMMG CSF concentration	
		$\beta$ (95% CI)	<i>P</i> value	$\beta$ (95% CI)	<i>P</i> value
Albumin ratio ( $\times 10^{-3}$ )	per 10 unit increase	1.499 (1.290–1.709)	<0.0001	0.388 (0.356–0.421)	<0.0001
Lag time dose to sampling (h)	per 1 unit increase	–0.779 (–1.350 to –0.208)	0.015	–0.046 (–0.072 to –0.020)	0.0038
Creatinine clearance (mL/min)	per 10 unit increase	–1.428 (–2.099 to –0.756)	0.0015	–0.161 (–0.245 to –0.077)	0.0027
Dose (mg/kg)	per 1 unit increase	1.703 (1.215–2.190)	<0.0001	0.093 (0.022–0.163)	0.017
Weight (kg)	per 10 unit increase	1.996 (1.000–2.991)	0.0005	0.223 (0.052–0.394)	0.013
Age (years)	per 10 unit increase	0.042 (–1.402 to 1.487)	0.95	–0.026 (–0.198 to 0.147)	0.74
Gender	women versus men	0.774 (–2.276 to 3.824)	0.60	0.292 (–0.179 to 0.762)	0.21

**Figure 2.** Aciclovir concentrations in serum ( $n=32$ ) and CSF ( $n=34$ ) samples from patients ( $n=21$ ) treated with aciclovir for herpesvirus CNS infection. (a) Increased CSF:serum albumin ratio, interpreted as an indication of BBB damage, is associated with increased aciclovir CSF concentrations. The dotted vertical line represents the upper normal reference for CSF:serum albumin ratio (10.2). (b) Decreased creatinine clearance, calculated using the Cockcroft–Gault formula, is associated with increased aciclovir serum and CSF concentrations. (c) Increasing dose of aciclovir is associated with increased aciclovir serum and CSF concentrations.

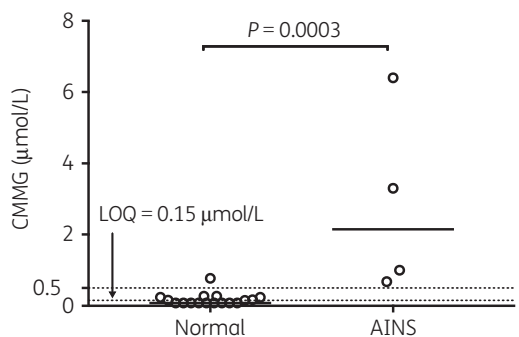
disease. Since the morbidity after herpesvirus CNS disease is considerable, it is still possible that some patients may tolerate and benefit from increased doses of aciclovir. However, the recommendation of doses  $>10$  mg/kg q8h in the initial stages of disease is debatable and should perhaps be reconsidered. Instead, it would be safer to consider an increase in dose after a few days of treatment, allowing time for adequate hydration

and assurance of stable renal function, as well as factoring in the CSF:serum albumin ratio to identify patients who present with less-pronounced BBB damage, or patients in which the BBB heals over the course of treatment.

In summary, patients with compromised BBB, decreased renal function and high aciclovir doses have an increased risk of accumulating CMMG in the CSF, and increased concentrations of CMMG



**Figure 3.** CMMG concentrations in serum ( $n=32$ ) and CSF ( $n=34$ ) samples from patients ( $n=21$ ) treated with aciclovir for herpesvirus CNS infection. (a) Increased CSF:serum albumin ratio, interpreted as an indication of BBB damage, is associated with increased CMMG CSF concentrations. The dotted vertical line represents the upper normal reference for CSF:serum albumin ratio (10.2). The dotted horizontal line represents a CMMG CSF concentration of  $0.5 \mu\text{mol/L}$ , previously associated with AINS. (b) Decreased creatinine clearance, calculated using the Cockcroft–Gault formula, is associated with increased CMMG serum and CSF concentrations. The dotted horizontal line represents a CMMG CSF concentration of  $0.5 \mu\text{mol/L}$ , previously associated with AINS. (c) Increased dosing of aciclovir is associated with increased CMMG serum and CSF concentrations. The upper dotted horizontal line represents a CMMG serum concentration of  $10 \mu\text{mol/L}$ , previously associated with AINS, and the lower dotted horizontal line represents a CMMG CSF concentration of  $0.5 \mu\text{mol/L}$ , previously associated with AINS.



**Figure 4.** Comparison of peak CMMG concentrations in CSF samples from patients ( $n=21$ ) treated with aciclovir for herpesvirus CNS infection. Comparison is made between patients with ( $n=4$ ) and without ( $n=17$ ) suspected AINS, previously associated with CMMG  $>0.5 \mu\text{mol/L}$  (upper dotted horizontal line). Bar is set at the median. The lower dotted horizontal line represents the CMMG analysis limit of quantification (LOQ) of  $0.15 \mu\text{mol/L}$ .

are associated with AINS. To optimize aciclovir dosing, we suggest that it may be advantageous to reconsider treatment with doses  $>10 \text{ mg/kg q8h}$ , analyse CSF:serum albumin ratios in

addition to evaluation of renal function, and, when available, measure CSF concentrations of both aciclovir and CMMG. This approach may be of particular interest when trying to discriminate between AINS and aggravated symptoms due to viral CNS disease.

### Acknowledgements

We thank our colleagues and staff at the Department of Infectious Diseases at Sahlgrenska University Hospital, Gothenburg, for helpful assistance in including the patients in this study.

### Funding

The study was financed by grants from the Swedish state under the agreement between the Swedish government and the country councils, the ALF-agreement (#ALFBGB-74050).

### Transparency declarations

None to declare.

## Supplementary data

A Case Series is available as [Supplementary data](#) at JAC Online.

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