JICNA® Journal of the International Child Neurology Association
A peer reviewed open access e-journal in Child Neurology

OPEN ACCESS
ORIGINAL RESEARCH

The association between human herpes viruses and acute symptomatic seizures in Kenyan children

Symon M Kariuki[1,2],* Christian Schubart[3], and Charles RJC Newton[1,2]

[1]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya; [2] Department of Psychiatry, University of Oxford, UK; [3] Department of Psychiatry, Tergooi Hospital, Hilversum, the Netherlands

Email addresses: Symon M Kariuki (skariuki@kemri-wellcome.org); Christian Schubart (cdschubart@gmail.com); Charles RJC Newton (cnewton@kemri-wellcome.org)

Corresponding author: Symon M Kariuki; Email: skariuki@kemri-wellcome.org

ABSTRACT

In malaria-endemic areas, where up to 70% of children have peripheral parasitaemia, it is unclear why some children develop seizures. Human herpes viruses are a common cause of seizures with fever, but their role in acute symptomatic seizures is not fully understood. We investigated the hypothesis that acute symptomatic seizures in children admitted to hospital are caused by concomitant human herpes virus infections.

We examined the presence of parasitaemia in plasma and viruses in the cerebrospinal fluid (CSF) of 100 children with acute symptomatic seizures (84%) and with complex acute symptomatic seizures (focal, repetitive or prolonged), and in 45 children without seizures, using polymerase chain reaction. The analysis compared the distribution of the human herpes virus between children with acute symptomatic seizures and those without these seizures, by computing odds ratios using a logistic regression, accounting for potential confounders.

Human herpes viruses (HHV) 6 and 7 were found in the CSF of 22% of children with acute symptomatic seizures and in 24% of those without seizures, and overall, positivity for any of the viruses was not associated with acute symptomatic seizures or complex acute symptomatic seizures. HHV 7 was significantly associated with complex acute symptomatic seizures (OR=8.80 (95%CI, 1.20-64.84), p=0.033), while HHV 6 was not (OR=1.71 (95%CI, 0.55-5.30), p=0.351). The OR for the association of HHV 7 with complex acute symptomatic seizures increased by 81% (from 4.87 to 8.80) after accounting for falciparum malaria, malnutrition and CSF protein levels.

HHV 7 but not 6 is associated with common complex acute symptomatic seizures in a malaria-endemic area in Kenya, and this association may be moderated by malaria, nutrition status and protein leVels. Children admitted with acute symptomatic seizures should be screened for viruses.

Keywords: acute symptomatic seizures, children, human herpes viruses, falciparum malaria

BACKGROUND

Acute symptomatic seizures are a common presentation in children admitted to hospitals in sub-Saharan Africa[1]. Falciparum malaria remains the commonest cause of acute symptomatic seizures in malaria-endemic areas[2], and these seizures often have complex features: focal (involving a body part), repetitive (>two seizures in 24 hours) or prolonged (lasting >15 minutes)[3]. However, because the prevalence of asymptomatic parasitaemia in the community is high (up to 70%) in these areas[4], other childhood illnesses (e.g. viral or bacterial) may be important causes of acute symptomatic seizures, with the presence of malaria parasitaemia being coincidental. We showed through modelling that about 10% of acute symptomatic seizures in malaria may indeed be attributable to other illnesses[2], which may include central nervous system (CNS) infections with viruses and bacteria.

HHV 6 was isolated in 23% of children with acute symptomatic seizures in the USA[5], but it is not clear if this virus caused these seizures since there was no comparison with a control group. Another study of acute symptomatic seizures did not isolate human herpes viruses[6], as would be expected of seizures without neurological damage. Acute symptomatic seizures in malaria-endemic areas are likely to be related to direct brain involvement, e.g. sequestration of *P. falciparum* parasites[2], but may also be caused by a concomitant viral infection, as documented in previous studies[7,8].

These viral aetiologies of fever have increased recently following the decline of malaria[9] and should be screened for in children admitted to hospitals in endemic areas. Recently, we observed that the incidence of acute symptomatic seizures without a known cause is increasing[10], an increase that could, in part, be due to neurotropic viral infections. However, the diagnosis of viral infections of the CNS is problematic since blood tests for antibodies to the virus only indicate exposure to the virus, and cerebrospinal fluid

(CSF) can only be collected from children who have a clinical indication for a lumbar puncture. Polymerase chain reactions (PCR) can detect the DNA of herpes viruses in the CSF of children and provide a more reliable indicator of CNS infection[11]. The CSF can be obtained from children who require a lumbar puncture, to exclude treatable infections, particularly bacterial meningitis.

We tested the hypotheses that herpes viruses are associated with the risk of acute symptomatic seizures in children admitted to a rural hospital in a malaria-endemic area on the Kenyan coast. We also examined whether the associations between human herpes viruses are moderated by other potential confounders, in particular falciparum malaria.

METHODS

We studied 145 children admitted to Kilifi District Hospital (KDH) with acute non-traumatic encephalopathy between 1999 and 2001. This data was collected prospectively, but only analysed sometime later, post the malaria-decline period, when the role of neurotropic viruses in CNS disease was increasingly being recognised[7,10]. KDH is the only referral hospital in Kilifi County. The hospital has a 35-bed paediatric ward and six-patient high dependency unit, which admits children with infections such as malaria and related complications.

PCR was successfully performed in the CSF of all 145 children admitted with acute non-traumatic encephalopathy, using a method we have described elsewhere[11]. We excluded children with head injury and those with epilepsy from these analyses. Bacterial meningitis was excluded according to previously reported criteria[12]. Peripheral parasitaemia was detected using thin and thick blood slides on Giemsa stain. The total protein in CSF was measured by turbidimetry using benzethonium chloride as described elsewhere[13]. Albumin was measured using an electroimmunoassay technique[14].

Viruses were looked for in two distinct groups of children with encephalopathy; (i) 100 children admitted with acute symptomatic seizures and coma (inability to localise a painful stimulus[15]) and (ii) 45 children with coma but without seizures during the current illness.

The student's t-test or the Mann-Whitney test (where appropriate) was used to compare continuous variables. Dichotomous variables were compared using Pearson's chi square or Fisher's exact test where appropriate. Logistic regression was used to compute measures of association between acute symptomatic seizures and the presence of herpes viruses, accounting for: (i) age and sex initially; (ii) other potential confounders, e.g. CSF protein levels and malnutrition, in a penultimate model; and (iii) falciparum malaria in the final model. The logistic models were done systematically, so that the final model had all the variables accounted for in situ. Weight for age z-scores were computed using the zanthro command on Stata (2000 CDC Growth Reference in the USA).

RESULTS

HHV 6 was found in the CSF of 19% of 145 children with encephalopathy, while HHV 7 was found in 7%. Both viruses were present in the CSF of four children. Malaria parasitaemia was detected in 48% of the 100 children admitted with acute symptomatic seizures, and none in those without seizures (X^2=32.1, P<0.001) (Table 1). Among the 100 children with seizures, HHV 6 was found in 16%, and HHV 7 in 8%. Of the children admitted with encephalopathy, human herpes viruses were present in 22% of the 100 children with acute symptomatic seizures, and in 24% of those without seizures (Table 1). The complex acute symptomatic seizures occurred in 8/10 (80%) of cases with the human herpes 7 viruses and in 15/27 (56%) of cases with the human herpes 6 viruses.

Children admitted with acute symptomatic seizures were older (p<0.001), febrile (p=0.008), less likely to be jaundiced (p<0.001), less likely to be malnourished (p<0.001), more likely to have a lower CSF protein (p<0.001) and a higher haemoglobin concentration (p<0.001), and were less likely to die (p<0.001), compared to those without seizures (Table 1). Most clinical and laboratory characteristics and outcomes were similar between children admitted with acute symptomatic seizures with HHV 6 and 7, and those with seizures without these viruses (Table 2).

The combined human herpes viruses were not associated with acute symptomatic seizures in a logistic regression model with age and sex as covariates (OR=1.48 (95%CI, 0.54-4.05), p=0.448). After further accounting for malnutrition and CSF protein levels (the non-febrile features with statistically significant differences between those with acute symptomatic seizures and no seizures (0.2g/dl vs. 0.5g/dl, respectively; p<0.001) (Table 1)), the association between human herpes viruses and acute symptomatic seizures was still not statistically significant (OR=1.30 (95%CI, 0.38-4.47), p=0.679). In a final model, additionally accounting for falciparum malaria, the combined human herpes viruses were not associated with acute symptomatic seizures (OR=1.27 (95%CI, 0.37-4.35), p=0.705).

We repeated the acute symptomatic seizures analysis separately for each virus. No acute symptomatic seizures were associated with HHV 7 (OR=2.94 (95%CI, 0.48-18.11), p=0.244), nor with HHV 6 (OR=1.19 (95%CI, 0.41-3.41), p=0.750), in a model accounting for age and sex. Accounting for malnutrition and CSF protein levels was significantly associated with acute symptomatic seizures for HHV 7 (OR=5.08 (95%CI, 0.65-39.78), p=0.122), but not HHV 6 (OR=0.87 (95%CI, 0.23-3.29), p=0.842). After additional inclusion of falciparum malaria into the model, acute symptomatic seizures remained associated with HHV 7 (OR=4.62 (95%CI, 0.58-36.46), p=0.147), but not with HHV 6 (OR=0.94 (95%CI, 0.26-3.42), p=0.929).

We repeated the above analysis for complex acute symptomatic seizures, which were particularly associated with falciparum malaria in this study (OR=4.68 (95%CI, 1.69-13.01), p=0.003), and in a previous study[2]. Human herpes viruses combined were poorly associated with complex acute symptomatic seizures in a logistic regression model with age and sex as covariates, but the association was not statistically significant (OR=2.34 (95%CI, 0.92-5.97), p=0.075). After further accounting for malnutrition and CSF protein levels (significant features in Table 1), which are not febrile causes of complex acute symptomatic seizures, the OR point improved by 6%, but the association was not statistically significant (OR=2.48 (95%CI, 0.83-7.43), p=0.104). In a final model additionally accounting for falciparum malaria, the association of human herpes viruses with acute symptomatic seizures was unchanged (OR=2.47 (95%CI, 0.83-7.36), p=0.103).

We repeated the analysis of complex acute seizures, again using the viruses separately. There was no significant

association between complex acute symptomatic seizures and HHV 7 (OR=4.87 (95%CI, 0.86-27.53), p=0.074), nor with HHV 6 (OR=1.74 (95%CI, 0.65-4.67), p=0.271), in a model accounting for age and sex. Additionally, accounting for malnutrition and CSF protein levels was significantly associated with complex acute symptomatic seizures for HHV 7 (OR=9.22 (95%CI, 1.25-68.27), p=0.030), but not for HHV 6 (OR=1.64 (95%CI, 0.52-5.19), p=0.396). After additional inclusion of falciparum malaria into the model, complex acute symptomatic seizures remained associated with HHV 7 (OR=8.80 (95%CI, 1.20-64.84), p=0.033), but not with HHV 6 (OR=1.71 (95%CI, 0.55-5.30), p=0.351). The OR for the significant final model for HHV 7 (OR=8.80) is greater than the baseline model (4.87) by 81%, suggesting evidence for effect modification of HHV 7 by falciparum malaria, malnutrition and CSF protein levels.

DISCUSSION

Neither HHV 6 or 7 was associated with acute symptomatic seizures or complex acute symptomatic seizures. However, HHV 7 was associated with complex acute symptomatic seizures, but not with all acute symptomatic seizures, in a model accounting for falciparum malaria, malnutrition and CSF protein levels. Accounting for proteins is justified, because it is thought they may have anti-convulsant effects on the brain tissues, possibly related to increased extracellular osmolality[16]. In fact, accounting for these three potential confounders improved the OR for the associations by 81%. On the contrary, HHV 6 was not associated with any acute symptomatic seizures, nor complex acute symptomatic seizures.

The prevalence of herpes viruses detected in the CSF of children with encephalopathy or acute symptomatic seizures in this study was high (23%), and was higher for HHV 6 (16%) than for HHV 7 (7%). The finding that HHV 6 is more common in acute seizures than HHV 7, is similar to findings from the American study on consequences of prolonged febrile seizures in childhood (FEBSTAT)[17]. The prevalence of the viruses detected in acute symptomatic seizures is similar to a study from the US (23%)[5], but lower than in a Malawian study (73%)[7]; probably because the latter study additionally screened for other arboviruses and adenoviruses, which were not assessed in the current study. Recent studies in similar poor-resource settings have recognised the role of viruses in the aetiology of acute encephalopathy[7]. Additionally, other studies in high-income countries have associated viruses with seizures[5,18]. These two viruses were however not isolated in an American study of seizures with fever[6], as would be expected, since these seizures do not have neurological involvement like the acute symptomatic seizures in our study. A recent study of acute symptomatic seizures[10] reported a high prevalence of undifferentiated causes of acute symptomatic seizures (4%), some of which could be viruses, therefore calling for the need to screen for the presence of viruses in admissions with acute symptomatic seizures. In a recent study conducted during the malaria-decline era[9], viral causes of encephalopathy caused more morbidity and mortality in Tanzanian children admitted to hospital (70%) than both parasitic (11%) and bacterial infections (22%) combined.

HHV 7 was associated with complex acute symptomatic seizures, but not acute symptomatic seizures, while the viruses combined were not associated with seizures. The lack of association in the combined group may have been driven by HHV 6, which individually did not show association with seizures. The finding that HHV 7 is more epileptogenic than HHV 6 is informative in that the pathogenesis of the two related viruses can be different, supported by documentation of more complex seizure phenotypes in the former than the latter viruses. Complex acute symptomatic seizures are more severe than simple seizures, so their association with HHV 7 may suggest a direct brain involvement by the virus that warrants further neuroimaging or electroencephalographic investigations. It is worth noting that the association was significant after accounting for falciparum malaria and malnutrition, protein levels, three of which modified the OR by 81%, suggesting they moderate the association between human herpes viruses and acute symptomatic seizures. We have previously shown that malaria is an important cause of acute symptomatic seizures in children admitted to hospital[1,2], and can interact with viruses to cause brain damage[8]. This hypothesis is also supported by the finding that both malaria and viruses were detected in 9% of acute symptomatic seizures, similar to the modelled proportion of about 10% that we found using a logistic regression technique[2]. Proteins depend on nutritional status and can moderate the viral association with acute symptomatic seizures by being pro-convulsant via reducing the bioavailability of anticonvulsants[19], or anticonvulsant through changing the extracellular osmolality[20], but further studies are required.

A limitation of this study was the relatively small sample size, which may reduce the capability to measure associations. Secondly, the prevalence of viruses in the hospital comparison group used in this study may differ from that of controls from the community. We did not screen for other viruses, such as adenoviruses and arboviruses, which are neurotropic. These results should be interpreted carefully owing to the small sample size.

This study shows that HHV 7 (which was less frequent than HHV 6) is associated with complex acute symptomatic seizures after accounting for potential confounders, but HHV 6 and both viruses combined are not associated with these seizures. The association is moderated by malaria, malnutrition and protein levels, since substantial effect modification of the OR was observed. These results suggest that human herpes viruses, including other neurotropic viruses not investigated in this study, should be screened for in children admitted with acute symptomatic seizures, particularly those that are complex. These findings are especially important post the malaria-decline era when other non-malaria causes of CNS diseases are increasingly being recognised[7,10]. Future studies are required to understand the role of protein levels and acute symptomatic seizures following CNS infections.

Acknowledgments

We thank the clinical and technical staff of the microbiology laboratory department of the KEMRI-Wellcome Trust Research Programme who made this study possible. Mary Bitta reviewed the manuscript, and we appreciate her invaluable help. This study was supported by the Wellcome Trust (through a Senior Clinical Fellowship (083744) to Prof. CRJC Newton). Symon Kariuki was supported by the Wellcome Trust (through a Research Training Fellowship (099782)) and the MQ fellows award. This paper is published with the permission of the director of the Kenya Medical Research Institute.

Competing interests

The authors have no competing interests to declare.

Author contributions

Symon M Kariuki analysed the data and wrote the first draft of the manuscript. Christian Schubart designed the study, performed PCR to identify viruses in CSF and revised the manuscript. Charles Newton conceived and designed the study and helped with data analysis and writing of the manuscript. All authors approved the final version of the manuscript.

Cite this article as:
Kariuki et al.: The association between human herpes viruses and acute symptomatic seizures in Kenyan children, JICNA 2018 18:64

REFERENCES

1. Idro R, Gwer S, Kahindi M, Gatakaa H, Kazungu T, Ndiritu M, Maitland K, Neville BG, Kager PA, Newton CR: **The incidence, aetiology and outcome of acute symptomatic seizures in children admitted to a rural Kenyan district hospital.** *BMC Pediatr* 2008, **8:**5.
2. Kariuki SM, Ikumi M, Ojal J, Sadarangani M, Idro R, Olotu A, Bejon P, Berkley JA, Marsh K, Newton CR: **Acute symptomatic seizures attributable to falciparum malaria in an endemic area on the Kenyan coast.** *Brain* 2011, **134:**1519-1528.
3. Waruiru CM, Newton CR, Forster D, New L, Winstanley P, Mwangi I, Marsh V, Winstanley M, Snow RW, Marsh K: **Epileptic seizures and malaria in Kenyan children.** *Trans R Soc Trop Med Hyg* 1996, **90:**152-155.
4. Snow RW, Omumbo JA, Lowe B, Molyneux CS, Obiero J-O, Palmer A, Weber MW, Pinder M, Nahlen B, Obonyo C, et al: **Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa.** *The Lancet* 1997, **349:**1650-1654.
5. Hall CB, Long CE, Schnabel KC, Caserta MT, McIntyre KM, Costanzo MA, Knott A, Dewhurst S, Insel RA, Epstein LG: **Human Herpesvirus-6 Infection in Children -- A Prospective Study of Complications and Reactivation.** *N Engl J Med* 1994, **331:**432-438.
6. Teach SJ, Wallace HL, Evans MJ, Duffner PK, Hay J, Faden HS: **Human herpesviruses types 6 and 7 and febrile seizures.** *Pediatr Neurol* 1999, **21:**699-703.
7. Mallewa M, Vallely P, Faragher B, Banda D, Klapper P, Mukaka M, Khofi H, Pensulo P, Taylor T, Molyneux M, Solomon T: **Viral CNS infections in children from a malaria-endemic area of Malawi: a prospective cohort study.** *Lancet Glob Health* 2013, **1:**e153-e160.
8. Newton CR: **Viral infections of the CNS in sub-Saharan Africa: interaction with Plasmodium falciparum.** *Lancet Glob Health* 2013, **1:**e121-122.
9. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, Lengeler C, Cherpillod P, Kaiser L, Genton B: **Beyond malaria--causes of fever in outpatient Tanzanian children.** *N Engl J Med* 2014, **370:**809-817.
10. Schubart CD, Mturi N, Beld MGHM, Wertheim PM, Newton CRJC: **Role of viruses in Kenyan children presenting with acute encephalopathy in a malaria-endemic area.** *The American Journal of Tropical Medicine and Hygiene* 2006, **75:**1148-1150.
11. O'Meara WP, Bejon P, Mwangi TW, Okiro EA, Peshu N, Snow RW, Newton CR, Marsh K: **Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya.** *Lancet* 2008, **372:**1555-1562.
12. Berkley JA, Mwangi I, Ngetsa CJ, Mwarumba S, Lowe BS, Marsh K, Newton CR: **Diagnosis of acute bacterial meningitis in children at a district hospital in sub-Saharan Africa.** *Lancet* 2001, **357:**1753-1757.
13. Luxton RW, Patel P, Keir G, Thompson EJ: **A micro-method for measuring total protein in cerebrospinal fluid by using benzethonium chloride in microtiter plate wells.** *Clin Chem* 1989, **35:**1731-1734.
14. McLean BN, Luxton RW, Thompson EJ: **A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the Log IgG-Index. A comparison and diagnostic applications.** *Brain* 1990, **113 (Pt 5):**1269-1289.
15. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A: **Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children.** *Q J Med* 1989, **71:**441-459.
16. Gamkrelidze N, Butsashvili M, Barabadze K, Kamkamidze G: **Rare recurrence of seizures in children with episodes of febrile seizures associated with herpesvirus 6 infection.** *Georgian Med News* 2006**:**88-90.
17. Serem GK, Newton CR, Kariuki SM: **Incidence, causes and phenotypes of acute symptomatic seizures in Kenyan children post the malaria-decline period.** *BMC Neurol* 2015, **15:**180.
18. Salar S, Maslarova A, Lippmann K, Nichtweiss J, Weissberg I, Sheintuch L, Kunz WS, Shorer Z, Friedman A, Heinemann U: **Blood-brain barrier dysfunction can contribute to pharmacoresistance of seizures.** *Epilepsia* 2014, **55:**1255-1263.
19. Saly V, Andrew RD: **CA3 neuron excitation and epileptiform discharge are sensitive to osmolality.** *J Neurophysiol* 1993, **69:**2200-2208.

Table 1: Clinical characteristics of children admitted with acute non-traumatic encephalopathy

Clinical characteristics	Acute symptomatic seizures (n=100)	No seizures (n=45)	P-value
Males (%)	53 (53.0%)	25 (55.6%)	0.775
Age in months: median (IQR)	12.1 (8.1-17.9)	<1 (<1-5.3)	<0.001
Examination on admission			
Weight (kg) for age (years) z-scores: mean (SD)	-2.2 (1.2)	-1.8 (1.3)	0.090
Axillary temperature (°C): mean (SD)	38.2 (1.5)	36.5 (5.7)	0.008
Mid-upper arm circumference (cm): median (IQR)	13.4 (12.4-14.4)	8.9 (6.4-11.2)	<0.001
Jaundice (%)	2 (2.0%)	10 (22.2%)	<0.001
Laboratory investigations			
Parasitaemia ($x10^6$/L): median (IQR)	21,069 (6,845-226,080)	-	-
Parasitaemia (%)	48 (48.0%)	-	-
Haemoglobin (g/dL): mean (SD)	8.2 (2.8)	12.0 (4.3)	<0.001
White blood cell count ($x10^9$/L): median (IQR)	11.9 (9.5-18.7)	14.45 (10.7-21.6)	0.219
Blood glucose (mmol/L): mean (SD)	5.1 (2.2)	4.4 (3.1)	0.090
Cerebrospinal fluid			
Both human herpes viruses (HHV) 6&7 (%)	22 (22.0%)	11 (24.4%)	0.745
HHV6 (%)	16 (16.0%)	11 (24.4%)	0.227
HHV7 (%)	8 (8.0%)	2 (4.4%)	0.434
White cell count (/mm^3)	2 (0.1-6.0)	2 (0.1-6.0)	0.435
Protein (g/dl): median (IQR)	0.2 (0.1-0.3)	0.5 (0.3-0.6)	<0.001
CSF/blood glucose ratio: median (IQR)	0.73 (0.6-0.8)	0.8 (0.6-1.0)	0.209
Outcome			
Neurological deficits (%)	1 (1.0%)	2 (7.4%)	0.060
Mortality (%)	1 (1.0%)	20 (44.4)	<0.001

CSF=cerebrospinal fluid; SD=standard deviation; IQR=interquartile range

Table 2: Clinical characteristics of acute symptomatic seizures associated with human herpes virus 6 & 7 and those not associated with these viruses

Clinical characteristics	Acute symptomatic seizures associated with HHV6&7 (n=22)	Acute symptomatic seizures not associated with HHV6&7 (n=78)	P-value
Males (%)	10 (45.5%)	43 (55.1%)	0.422
Age in months: median (IQR)	10.3 (6.5-14.5)	12.6 (8.3-18.9)	0.093
Examination on admission			
Weight (kg): mean (SD)	7.8 (2.5)	7.8 (2.0)	0.969
Axillary temperature (°C): mean (SD)	38.3 (1.4)	38.1 (1.5)	0.662
Mid-upper arm circumference (cm): median (IQR)	13.7 (12.6-15.0)	13.3 (12.4-14.2)	0.458
Jaundice (%)	1 (1.28%)	1 (4.6%)	0.393
Laboratory investigations			
Parasitaemia (x10^6/L): median (IQR)	178,200 (8,002-551,490)	16,728 (6,760-169,000)	0.136
Parasitaemia (%)	9 (40.9%)	39 (50.0%)	0.451
Haemoglobin (g/dL): mean (SD)	8.9 (3.0)	8.0 (2.7)	0.198
White blood cell count (x10^9/L): median (IQR)	13.4 (9.4-17.0)	11.6 (9.6-18.9)	0.956
Blood glucose (mmol/L): mean (SD)	4.7 (2.3)	5.3 (2.3)	0.271
Cerebrospinal fluid			
White cell count (/mm^3)	0.1 (0.1-6.0)	2 (0.1-6.0)	0.614
Protein (g/dl): median (IQR)	0.2 (0.1-0.3)	0.2 (0.3-0.3)	0.786
CSF/blood glucose ratio: mean (SD)	0.75 (0.21)	0.76 (0.26)	0.863
Acute symptomatic seizures			
Focal seizures	9 (40.9%)	31 (39.7%)	0.921
Convulsive status epilepticus	7 (31.8%)	21/77 (27.3%)	0.676
Repetitive seizures	14 (63.6%)	50 (64.1%)	0.968
All complex acute symptomatic seizures	21 (95.5%)	63 (80.8%)	0.097
Seizures on admission	3 (13.6%)	19/76 (25.0%)	0.261
Outcome			
Neurological deficits (%)	0 (0%)	1/75 (1.33%)	0.773
Mortality (%)	0 (0%)	1 (1.28%)	0.780

CSF=cerebrospinal fluid; HHV=human herpes virus; SD=standard deviation; IQR=interquartile range