The first reported cases of elephant endotheliotropic herpesvirus infectious haemorrhagic disease in Malaysia: case report

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Abstract

Background: Elephant endotheliotropic herpesvirus haemorrhagic disease (EEHV HD) is the leading cause of death in captive Asian elephant calves in Asia, North America, and Europe with a mortality rate of ~65% in calves that are under human care. Although EEHV HD was first found in elephant camps, more recently it was identified in wild populations which poses a greater threat to the elephant population. Deaths due to EEHV HD have been seen in wild elephants, but the in-situ prevalence and mortality rate is unknown. We report the first EEHV HD cases in Malaysia from 3 wild born endangered Bornean elephant calves from Sabah with known typical clinical signs.

Case presentation: The first calf died within 24 h of the onset of clinical signs; the second calf died within 12 h of the onset of clinical signs. The third calf succumbed within 72 h. Necropsies revealed that all 3 calves had similar presentations of EEHV HD but in the third calf with less severity. We conducted conventional polymerase chain reaction (cPCR) assays and found EEHV DNA at all 7 loci in the 3 calves; it was identified as EEHV1A, the virus type that has been found in most other reported cases.

Conclusion: Typical EEHV HD clinical signs and the molecular confirmation of EEHV by cPCR and sequencing point to EEHV as the cause of death. Further genetic investigation of the strain is in progress.

Keywords: Bornean elephant, Elephant endotheliotropic herpesvirus, Sabah, Malaysia
of EEHV HD, and five cases of barely clinical/subclinical EEHV, all due to either EEHV3A or EEHV3B, as well as a death from EEHV2 and what seems to have been a well-controlled viraemia from EEHV6 [17, Latimer E, personal communication]. Though the transmission mechanisms of EEHV have not been fully understood, viral DNA is found in trunk secretions and other bodily fluids and is believed to be involved in transmission [18].

EEHV-infected elephants display an acute onset of lethargy, generalised oedema of head and limbs, oral ulceration, cyanosis of the tongue, tachycardia, and death after a period of 1–7 days. Lymphopenia and thrombocytopenia are commonly seen in blood evaluations. Increasingly, there are reports of elephants surviving EEHV HD with treatment including antivirals, fluids, platelets, and immunostimulants, among other therapies [4, 17, 19–23]. Pericardial effusion, intestinal haemorrhage, and mucosal ulcerations are common necropsy findings. Target tissues for EEHV include heart, tongue, liver, and large intestine. Histological examinations usually reveal microhaemorrhages, oedema and inflammation in these organs. Lesions can be accompanied by intranuclear herpesvirus inclusions in capillary endothelial cells [1].

There is no prior report published of EEHV infection in Malaysia or from the Bornean elephant—a subspecies of Asian elephant on the island of Borneo, mainly in Sabah, a state in East Malaysia. Bornean elephants, *Elephas maximus borneensis*, are one of the four distinct subspecies of the Asian elephants. They are classified as endangered according to the International Union for Conservation of Nature (IUCN) Red list of threatened species due to habitat loss. More recently, the species is also threatened from illegal hunting, poisoning and attacks by those trying to protect crops. Sabah has an ex-situ population of 24 elephants in human care at the Sepilok Orangutan Rehabilitation Centre, (Sandakan, SORC), Borneo Elephant Sanctuary (Kinabatangan) and Lok Kawi Wildlife Park (Kota Kinabalu). The state’s wild population is estimated at 2000 individuals [24].

There are two hypotheses regarding the origins of these elephants—they were introduced to Borneo either from Sulu [25] or Sumatera and Peninsular Malaysia or were indigenous to Borneo but derived from a Sundaic stock [26]. Genetic studies of mitochondrial DNA divergence supports the latter hypothesis [26, 27]. In the wild, they can be found at the northern and north-eastern parts of Borneo in the state of Sabah in Malaysia and the upper Sembakung River in Kalimantan, Indonesia [28]. With the many rampant threats including EEHV HD, low population numbers and the uniqueness of the species in terms of its habitat range and genetic makeup, the conservation and the health of this species is tremendously important to ensure the survival of this iconic species in the wild and in human care.

**Case presentation**

The first occurrence of EEHV infection at SORC occurred in a 24-month-old *E. m. borneensis* calf (Table 1). Symptomatic treatment (prednisolone 1 mg/kg, papase, oxytetracycline 20 mg/kg, intravenous fluid therapy) was administered. The calf died within 24 h of the onset of clinical signs. Over 1 L of serosanguinous epicardial fluid

**Table 1** Details of the *E. m. borneensis* tested and their PCR results

| Animal         | Date and place of rescue | Sex | Age and weight during the outbreak | Date of initial disease signs | 1st collection (11 May 2016) | 2nd collection (25 May 2016) | PCR results with sequencing confirmation |
|----------------|--------------------------|-----|-----------------------------------|------------------------------|-------------------------------|-------------------------------|------------------------------------------|
| Jimbo (First case) | February 2014; Beluran, Sabah | Male | 24 months; 362 kg | 9th May 2016 | Not collected | Not collected | +* |
| Vinodh (Second case) | November 2014; Telupid, Sabah | Male | 24 months; 442 kg | 17th May 2016 | WB, S | WB, S | + |
| Tuntan (Third case) | February 2014; Sukau, Sabah | Male | 36 months; 478 kg | 20th May 2016 | WB, S | S | + |
| Danum | December 2015; Lahad Datu, Sabah | Male | 24 months; 289 kg | N/A | WB, S | S | − |
| Budak | February 2016; Kinabatangan, Sabah | Male | 5 months; 97.5 kg | N/A | WB, S | S | − |
| Tunku | February 2016; Kinabatangan, Sabah | Male | 5 months; 118 kg | N/A | WB, S | S | − |
| Adun | April 2015; Telupid, Sabah | Male | 12 months; 247 kg | N/A | WB, S | S | + |
| Dumpas | August 2015; Tawau, Sabah | Male | 21 months; 372 kg | N/A | WB, S | S | − |

WB, whole blood; S, serum; +, EEHV detected; −, EEHV not detected; N/A, not applicable
*PCR confirmation from organs, not from WB using subsequent PCR protocols only*
(Fig. 1D) was retrieved from the pericardial sac. The calf had facial swelling (Fig. 1A). Over 6–12 h the swelling increased, and discolouration of the tongue apex was observed (Fig. 1B). The necropsy revealed prominent facial and truncal oedema with cyanotic swollen tongue. Generalised subcutaneous petechiation (Fig. 1C) with moderate subcutaneous oedema was observed. Severe haemorrhaging was evident in the heart extending from the epicardium through the myocardium and papillary musculatures (Fig. 1E). Generalised haemorrhage and oedema along the gastrointestinal tract including the mesentery was observed (Fig. 1F), and the liver was enlarged with mild petechiation.

Following the first calf’s death, all other elephants at the SORC were administered acyclovir 19 mg/kg, oxytetracycline 20 mg/kg, vitamin C and virgin coconut oil supplements. The second EEHV case occurred 8 days later in another 24-month-old calf (Table 1). Intravenous fluid therapy was administered immediately, but the calf died less than 12 h later. The third death occurred 3 days later in a 36-month-old calf (Table 1). Treatment as described above was given. The calf regained appetite for milk and solid food the next day following intensive fluid therapy (rectal and intravenous). Nevertheless, on the next morning, the calf stopped eating and died several hours later.

The necropsy of the second dead calf revealed similar findings to the first one. The necropsy of the third calf showed similar findings to the first two calves but with less severity. Dullness, inappetence and lethargy were observed in all cases. While tongue cyanosis and swelling, and facial and trunk oedema were only observed in the first two calves. Vesicles and oral ulceration were not observed in all three calves.

Organ samples were collected from all three dead calves for Escherichia coli culture and histopathological examination. Blood samples from the last two dead calves and from five apparently healthy elephants from the SORC (Table 1) were stored and tested at the Wildlife Health, Genetic and Forensic Laboratory (WHGFL), Kota Kinabalu, Sabah, a certified biosafety level 2 laboratory, at the request of the Sabah Wildlife Department and with Sabah Biodiversity Centre approval (SaBC License Number: JKM/MBS.1000-2/2/LD.5). DNA was extracted from these samples using the QIAamp Blood and Tissue Mini Kit (Qiagen, Hilden, Germany). For immediate diagnosis, conventional PCR amplifications

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**Fig. 1** Necropsy findings of EEHV. **A** Marked facial and trunk oedema in the first case with tongue cyanosis. **B** Tongue discolouration due to internal haemorrhaging in the second case (also observed in the first case). **C** Diffuse subcutaneous petechiation observed in all 3 cases. **D** Pericardial effusion from the first case but present in all three cases. **E** Heart of the first case, severe cardiac haemorrhage. **F** Generalised haemorrhage of gastrointestinal tract observed in all 3 cases.
were conducted on the extracted DNA for herpesviruses using consensus [29, 30] and EEHV PCRs [4, 13] (Table 2). For further genetic investigations on the variabilities on these loci, all blood and organ samples were rescreened at WHGFL with PCRs on conserved gene loci—U60(TERex3), U71(gM), and U77(HEL) and on hypervariable gene loci—U48.5(TK), U48(gH-TK), U51(vGPCR1), and E54(vOX2-1) [Hayward G, unpublished data, 31] (Table 3). Since the serum and whole blood from the first dead calf were unavailable, initial consensus and EEHV PCRs were not performed for this animal. Instead, the organ samples were used for the subsequent EEHV PCRs.

Correct sized PCR products on electrophoresis agarose were excised and purified using the QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany). Purified products were sequenced using their corresponding specific primers. The nucleotide sequences were analysed with the Geneious 10.1.3 software (Auckland, New Zealand) and compared to sequences in GenBank for homology analysis using the Basic Local Alignment Search Tool (BLAST; National Center for Biotechnology Information). Cleaned sequences from the initial EEHV PCR were aligned with 17 published EEHV DNA polymerase sequences using the Geneious Prime 2021.1.1 software (Auckland, New Zealand) Geneious Alignment (Alignment type: Global alignment with free end gaps; Cost matrix: Identity, Table 4). Aligned sequences were used to build a phylogenetic tree using the Geneious Prime 2021.1.1 software (Auckland, New Zealand) Geneious Tree Builder, with the Jukes-Cantor genetic distance model and 1000 bootstrap replicates (Fig. 2).

Histopathological examination showed that inclusion bodies were insignificant in the organs of the three calves, but the histopathological lesions were suggestive of enteritis in the first calf and viral infection in the second and third. Using the consensus terminase and polymerase herpesvirus, the polymerase specific EEHV 3/4 and the EEHV terminase PCR assays, herpesvirus was not detected in all tested samples. Of the seven individuals from the SORC screened using the polymerase pan EEHV PCR assays, three individuals (second and third dead calves and one of the five healthy animals) were sequence-confirmed for EEHV, with 91–93% identical sequences to EEHV 1A and 1B (North American isolates) and elephantid herpesvirus

### Table 2 Initial diagnosis PCR protocols and primers used

| Target gene                               | Primer sequences (5'-3')                                                                                                                                                                                                 | Product length (bp) | References |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------|
| Terminus                                  | **Round 1:**
|                                           | TS‑TERM_707s: TTG TGG ACG AGR SIMAYT TYA T
|                                           | TS‑TERM_707as: ACA GCCACGC CGCNGTICCAIGC
|                                           | **Round 2:**
|                                           | TS‑TERM_708s: GCAAGACATCTTTYTITITTC T
|                                           | TS‑TERM_708as: TGTGCTGTGTRWAGCIGGRT                                                                                                                      | Round 1: 519         | [29]       |
|                                           |                                                                                                   | Round 2: 419         |            |
| Polymerase                                | **Round 1:**
|                                           | DFA: GAYTTYGCGAGGYNTAYC
|                                           | KG1: GTTTGCTACAGAGTCAAGA
|                                           | ILK: TCTGGCAACGACAGCGCAGGGT
|                                           | KG1: GTTTGCTCAAGAGTCAAGA                                                                                                                                   | Round 1: 900         | [30]       |
|                                           |                                                                                                   | Round 2: 215–315     |            |
| EEHV DNA Polymerase‑ Specific EEHV 3/4    | **Round 1:**
|                                           | 6719: CGTGAAGAGTGGTGCAAGAT
|                                           | 7400: CAGCTATCATCCAGGCTACAC
|                                           | 6720: AATCTGGCGCAGCTGCTGAC
|                                           | 6721: CTCACCTGCAACGCGCTCTA                                                                                                                                  | Round 1: 6719/7400: 390 | [13]       |
|                                           |                                                                                                   | Round 2: 6719/6720: 270 |            |
|                                           |                                                                                                   | Round 3: 6719/6721: 150 |            |
| EEHV DNA Polymerase‑ PAN EEHV and specific EEHV 6 | **Round 1:**
|                                           | 6710: ACAACACGCTGTGRTYTCYCCRTA
|                                           | 6711: GTATGTGATGYCAGNYGTYTAYCC
|                                           | 6712: TGYGGCGGTNTAYGATTYACGG
|                                           | 7584: CATCGATTGTTACCTTCATGGTC                                                                                                                                | Round 1: 6710/6711: 500 | [13]       |
|                                           |                                                                                                   | Round 2A: 6710/6712: 250 |            |
|                                           |                                                                                                   | Round 2B: 6711/7584: 500 |            |
|                                           |                                                                                                   | Round 3A: 6712/7584: 250 |            |
| EEHV DNA Terminase                        | **Round 1:**
|                                           | B1 LGH2425: ACACGCAACGGCTGTGRTYTCYCCRTA
|                                           | A2 LGH2428: TTGTTGAGGAGRNNAYTTYAT
|                                           | A3 LGH2426: GCAAGACATCTTTYTITITTC T
|                                           | B2 LGH2427: TGGTGGTGTRWANGCGNGRTC                                                                                                                           | Round 1: B1/A2: 575  | [4]         |
|                                           |                                                                                                   | Round 2: A3/B2: 415 A3SEQ/B2SEQ: 360 |            |
DNA polymerase. Phylogenetic analysis showed that there was 100% sequence agreement within the three calves with the initial EEHV PCR detection and they were more related to EEHV 1A from Lao (Accession no. KJ400033.1) than the other sequences used for the comparison. The EEHV detection for the first dead calf was confirmed with sequences from the follow-up PCRs. The detailed analysis of the results from the follow-up genetic investigations will be presented in a subsequent manuscript.

Discussion and conclusions
These are the first reported cases anywhere of EEHV HD in Bornean elephants (Elephas maximus borneensis). However, the lack of previous reports in Malaysia does not necessarily indicate a low EEHV HD morbidity.

Table 3  Subsequent PCR protocols and primers used

| Genes/loci | Primer sequences (5′-3′) | Product length (bp) | Accession number |
|------------|--------------------------|---------------------|------------------|
| U60(TErEx3) | LGH6640: AAA GTT TCTAT CTC GGA TAC | Round 1: 6640/6672 | JX011056-62 |
|            | LGH6672: CAT GTT GAG CGG CAT CTC T | Round 2: 6640/6712 | |
| U71(gM)    | LGH6749: CT TGG TAT CTT AGC TAC | Round 1: 6749/6752 | JX011063-71 |
|            | LGH6752: CT ACC GGG CAT CAC TAG | Round 2: 6640/6712 | |
| U77(HEL)   | LGH6743: GC AAG GTC ACT TCC TGG | Round 1: 6732/6742 | JX011072-79 |
|            | LGH6742: CA CA GAC TCG CAT CTG | Round 2: 6640/6712 | |
| U48.5(TK)  | LGH6764: GCA GCT TAC CAC GTA CTC | Round 1: 6732/6742 | |
|            | LGH7968: GCG TAC GAC GTC CAT C | Round 2: 6732/6742 | |
| U48(gH-TK) | LGH7981: CTR AT TMA AAT AGT GAA GAT | Round 1: 7981/7985 | JX011039-46 |
|            | LGH7985: GT TTA GCT TCC TCT TAT TTA | Round 2: 7981/7985 | |
| US1 (vGPCR1) | LGH7506: GAT TGA AAG GCC CAT GAT GTG | Round 1: 7981/7985 | JX011047-55 |
|            | LGH7506: GAT TGA AAG GCC CAT GAT GTG | Round 2: 7981/7985 | |
| E54(VOX2-1) | LGH8471: AT CCT CAG AAAG TAC AGT GTC | Round 1: 8471/8472 | MF464882-899 |
|            | LGH8472: GT TGG GCC CAC AGT CTT CAG | Round 2: 8471/8472 | |

Table 4  Cleaned sequences of the initial PCR of pan EEHV DNA polymerase, Round 2A using 6710/6712 [13]

| Accession number and sample name | Sequence (length in bp) |
|----------------------------------|-------------------------|
| OK635292 Adun S                  | TTGAACT CTTA AGCTCAC CCGCAGCTAA ACTAGTTT GGAGCATTTT GCCTTAAAGAC GTCAAATCTGTCTC GAATATATATGC | |
| OK635292 Vinodh S                | TCGTATTT TTTTAT TTTTATT TAAAGAC GTCAAATCTGTCTC GAATATATATGC | |
| OK635294 Tunstan S2               | CATGATTT TTTTAT TTTTATT TAAAGAC GTCAAATCTGTCTC GAATATATATGC | |
| OK635295 Vinodh WB2              | TCGTATTT TTTTAT TTTTATT TAAAGAC GTCAAATCTGTCTC GAATATATATGC | |

1 DNA polymerase. Phylogenetic analysis showed that there was 100% sequence agreement within the three calves with the initial EEHV PCR detection and they were more related to EEHV 1A from Lao (Accession no. KJ400033.1) than the other sequences used for the comparison. The EEHV detection for the first dead calf was confirmed with sequences from the follow-up PCRs. The detailed analysis of the results from the follow-up genetic investigations will be presented in a subsequent manuscript.

Discussion and conclusions
These are the first reported cases anywhere of EEHV HD in Bornean elephants (Elephas maximus borneensis). However, the lack of previous reports in Malaysia does not necessarily indicate a low EEHV HD morbidity.
Initially, EEHV was hypothesised to be a novel virus for Asian elephants spread via exposure to African elephants in captivity [2]. However, in 2012, Asian elephants were shown to be the host with detection in wild Indian elephants [3] as well as other subsequent detections of EEHV in wild and camp elephants in Asia [9, 31]. Our cases support the latter, as the affected animals had no prior contact with African elephants.

Shedding by herd members could be the source of infection in vulnerable calves; the source of the SORC outbreak is not known. The EEHV may have been shed by the two youngest calves, aged less than 12 months old rescued four months prior to the outbreak, that may have still been protected by maternal antibodies. The calves that died were older than 24 months; none of the younger calves exhibited any clinical signs, although...
EEHV was detected in one of them. This is consistent with other fatal cases in individuals above 24 months old [4, 10], with maternal antibodies generally waning by 24 months old, explaining the higher fatality in slightly older calves [32].

Most fatal EEHV HD cases are of juvenile Asian elephants, ranging from 12 to 84 months old and usually dying within 24 h of the first detectable clinical signs [2, 10]. The course of the disease in the first two calves was peracute, both dying in less than 24 h from the onset of clinical signs, the third calf died after 72 h. Viraemia can occur several days prior to the onset of clinical signs and by this time severe vascular lesions would have developed [10]. Nevertheless, keepers should still be trained to identify the signs of the disease. Immediate administration of antiviral drugs might prevent further vascular damage, but its efficacy remains unclear and needs more investigation [23, 33]. A symptomatic treatment regime, including intensive fluid therapy, anti-inflammatories, parenteral antibiotics, and vitamins, remains crucial to reduce or stop the effects of initial vascular damages [33]. The efficacy of lauric acid found in the virgin coconut oil given to the elephants for its supposedly antiviral properties [34] in the treatment of EEHV HD is inconclusive because we were not able to distinguish between the effects from the drug treatments and from the supplements. At the time of the outbreak, there was limited information available on successful treatments, new treatment guidelines published subsequently [19–23] provide useful guidance for future outbreaks.

Since this was the first time we found EEHV in our elephants, it is important to determine the prevalence, patterns of shedding and the duration of the disease. In addition, early detection by PCR is vital for preclinical viraemia detection; routine screening serves as an early warning system to better prepare elephant centres for managing imminent EEHV outbreaks. PCR monitoring after an outbreak event is also crucial. These approaches can help us to understand EEHV HD to reduce morbidity and mortality in wild and captive elephants that are already endangered through habitat loss and increasing conflict with humans.

Abbreviations
EEHV HD: Elephant endotheliotropic herpesvirus haemorrhagic disease; cPCR: Conventional polymerase chain reaction; IUCN: International Union for Conservation of Nature; SORC: Sepilok Orangutan Rehabilitation Centre; Sandakan, Sabah; WHGFL: Wildlife Health, Genetic and Forensic Laboratory, Kota Kinabalu, Sabah; SaBC: Sabah Biodiversity Center; BLAST: Basic local alignment search tool.

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Authors’ contributions
MHL advised on the testing, processed the samples, performed PCR assays, analysed and interpreted sequences and was a major contributor in preparing the manuscript. SKSSN supervised the necropsies, identified the disease from the signs, recommended treatment and contributed to writing the manuscript. LB and PN performed on-site clinical management on the sick elephants, necropsies, collected the samples and contributed to writing the manuscript. EL performed some of the PCR assays, analysed and interpreted sequences and was a major contributor in preparing the manuscript. DR arranged the logistics of samples to the lab and EL’s travel to and around Sabah and helped managed the outbreak. TH advised on sample collection and testing, supported herpesviruses testing using consensus PCR and first round of specific EEHV testing, arranged approval for lab testing and was a major contributor in preparing the manuscript. JRAS oversaw the operations of the SORC and WHGFL and contributed to writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
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Not applicable.
Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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