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CASE REPORT

First Human Case of Fatal *Halicephalobus gingivalis* Meningoencephalitis in Australia

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***Halicephalobus gingivalis* (previously *Micronema deletrix*) is a free-living nematode known to cause opportunistic infections, mainly in horses. Human infections are very rare, but all cases described to date involved fatal meningoencephalitis. Here we report the first case of *H. gingivalis* infection in an Australian human patient, confirmed by nematode morphology and sequencing of ribosomal DNA. The implications of this case are discussed, particularly, the need to evaluate real-time PCR as a diagnostic tool.**

CASE REPORT

A 74-year-old lady from a regional town in the Eyre Peninsula of South Australia with a 4-day history of mental state deterioration, fever, and a loss of coordination was transferred to the Royal Adelaide Hospital. She was moderately immune suppressed by methotrexate and etanercept treatment for rheumatoid arthritis and had a history of diabetes. During the admission, her conscious state deteriorated rapidly, requiring mechanical ventilation and admission to the intensive care unit (ICU). Subsequently, she developed signs of brainstem involvement and exhibited a loss of corneal and gag reflexes. She was administered benzylpenicillin, ceftriaxone, and aciclovir for presumptive meningoencephalitis of bacterial or viral etiology. Cerebrospinal fluid (CSF) obtained by lumbar puncture demonstrated 280 $\times 10^6$ polymorphonuclear leukocytes (PMN)/liter, 18 $\times 10^6$ mononuclear lymphocytes/liter, elevated CSF protein of 1.59 g/liter, and CSF glucose of 3.3 mmol/liter; aerobic and anaerobic bacterial culture results were negative, as were PCR results for *Streptococcus pneumoniae*, *Neisseria meningitidis*, herpes simplex virus, and varicella-zoster virus. CSF India ink stain and cryptococcal antigen lateral flow assay (Immy, Inc., Norman, OK, USA) results were negative. Magnetic resonance imaging (MRI) of the brain exhibited a left-predominant, asymmetrical meningeal enhancement in the frontoparietal cortex, without any detectable brainstem changes. Two days later, repeated lumbar punctures showed a marked elevation of PMN to 2,500 $\times 10^6$ cells/liter and 34 $\times 10^6$ mononuclear cells/liter, with no bacteria detected upon Gram staining. CSF stained with Diff-Quick (Alere, Brisbane, Australia) showed 99% PMN with very few eosinophils. CSF protein was markedly elevated (5.46 g/liter), and CSF glucose was 1.3 mmol/liter. Microscopic examination of 100 μl of unstained CSF was performed after centrifugation at 700 $\times$ *g* for 10 min, but no amoebic trophozoites were detected. With a suspicion of parasitic infection, given the unexplained high PMN counts, the antimicrobial treatment strategy was changed to liposomal amphotericin B, sulfadiazine, pentamidine, and azithromycin to target protists such as amoebae and *Toxoplasma gondii*. CSF was subjected to PCR for *Naegleria fowleri*, *Acanthamoeba* sp., and *Balamuthia mandrillaris*, but all test results were negative. No anti-*Strongyloides* serum antibody (IgG) was detected in an enzyme-linked immunosorbent assay using somatic larval antigens from *Strongyloides ratti* (Bordier Affinity Products) (1, 2). At day 7 of admission, the patient died following a complete loss of brainstem functions.

An etiological diagnosis was made based on postmortem findings. Microscopy of CSF and brain tissue exhibited numerous motile nematodes containing oval, elongated, thin-shelled, colorless eggs of 40 to 55 μm by 20 to 25 μm in size (average of 10 eggs) (Fig. 1). The larvae in CSF were 250 to 300 μm long and 15 to 20 μm wide, with a rhabditoid esophagus (70 to 90 μm long). Larvae from CSF were cultured using a modified *Strongyloides* agar plate culture method by replacing fecal material with an *Escherichia coli* ATCC 25922 suspension together with 100 μl of CSF onto the middle of a Mueller-Hinton agar plate (Oxoid, Australia) (3, 4). Every 7 days, new plates were inoculated. *E. coli* grew in tracks created by motile nematodes as they moved out of the central inoculum, and microscopic examination revealed nematodes at different stages of development (Fig. 2). Only female adult worms were observed; they possessed didelphic reproductive tracts and reflexed ovaries at the posterior end, consistent with the description of *Halicephalobus gingivalis* (5). The live nematodes were fixed in ethanol. Subsequently, DNA was isolated from individual worms and subjected to PCR-based sequencing of nuclear large-subunit ribosomal DNA (LSU rDNA) (6). The sequences deter-

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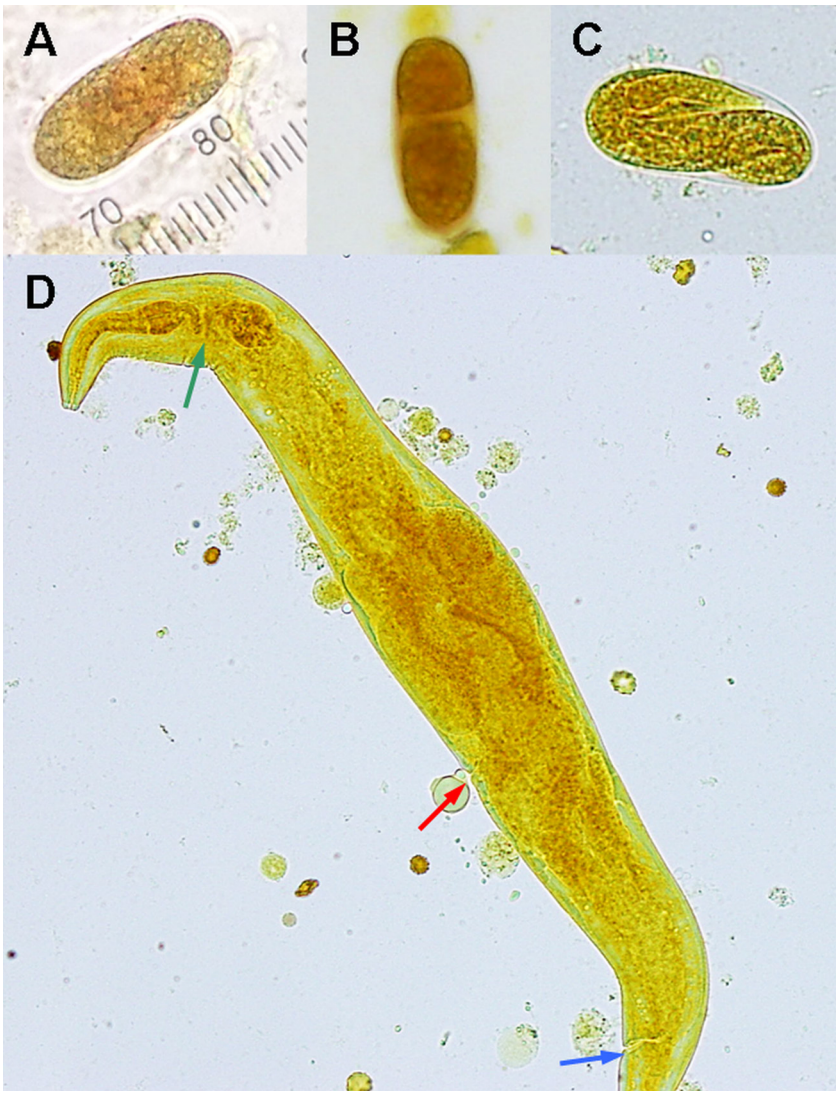

FIG 1 (A to C) Iodine stain of CSF obtained postmortem shows different stages of *H. gingivalis* egg development. (A) Single-cell stage (1 scale unit = 2.5 μm). (B) Two-cell stage. (C) Larval stage. (D) Iodine stain of a fourth-stage larva (300 μm in length) demonstrates a short buccal cavity, nerve rings (green arrow) between two bulbs of the rhabditoid esophagus, reflexed ovary, presence of vulva (red arrow), and anal pore (blue arrow).

mined from four individual nematodes were all the same and had 99% homology (1,385/1,399 bases) to that of *H. gingivalis* SAN100, isolated from a horse in Guelph, Canada (GenBank accession no. AY293177.1 [7]).

A complete postmortem examination was conducted, and a study of the brain revealed congested leptomeningeal blood vessels without significant opacity of the leptomeninges or CSF. The brain had a normal weight of 1,160 g, and there was no significant cerebral edema. There was extensive brain necrosis, primarily affecting the temporal lobes (bilaterally) and the right and left basal ganglia, anterior corpus callosum, right cerebral peduncle, and cerebellum. Histopathological examination of the brain showed meningoencephalitis, with mild to moderate perivascular inflammation comprising lymphocytes and macrophages and with no evidence of granulomatous inflammation (Fig. 2). The inflammation extended into the brain parenchyma, and there were multiple foci of necrosis and widespread cortical hypoxic-ischemic injury characterized by neuronal red cell change. Adult female nematodes, larvae, and eggs were observed in every section of the brain (bilateral hemispheres, cerebellum, brain stem, pituitary gland, and leptomeninges), primarily in the perivascular spaces, including areas within the brain parenchyma in which the presence of *H. gingivalis* was identified without any apparent associated inflammatory response. The spinal cord was not examined. The nematode was not observed in any other organs (including heart, lungs, liver, and kidneys).

H. gingivalis belongs to the nematode family Paragrolaimidae. Currently, there are eight described species of *Halicephalobus*, and only *H. gingivalis* has been reported to infect humans and equines, predominantly horses (5) (Table 1 and Table 2). Only female worms have been isolated from parasitized hosts, confirming that *H. gingivalis* can reproduce parthenogenetically, although how *H. gingivalis* infects human and equine hosts is unknown (8–12). In

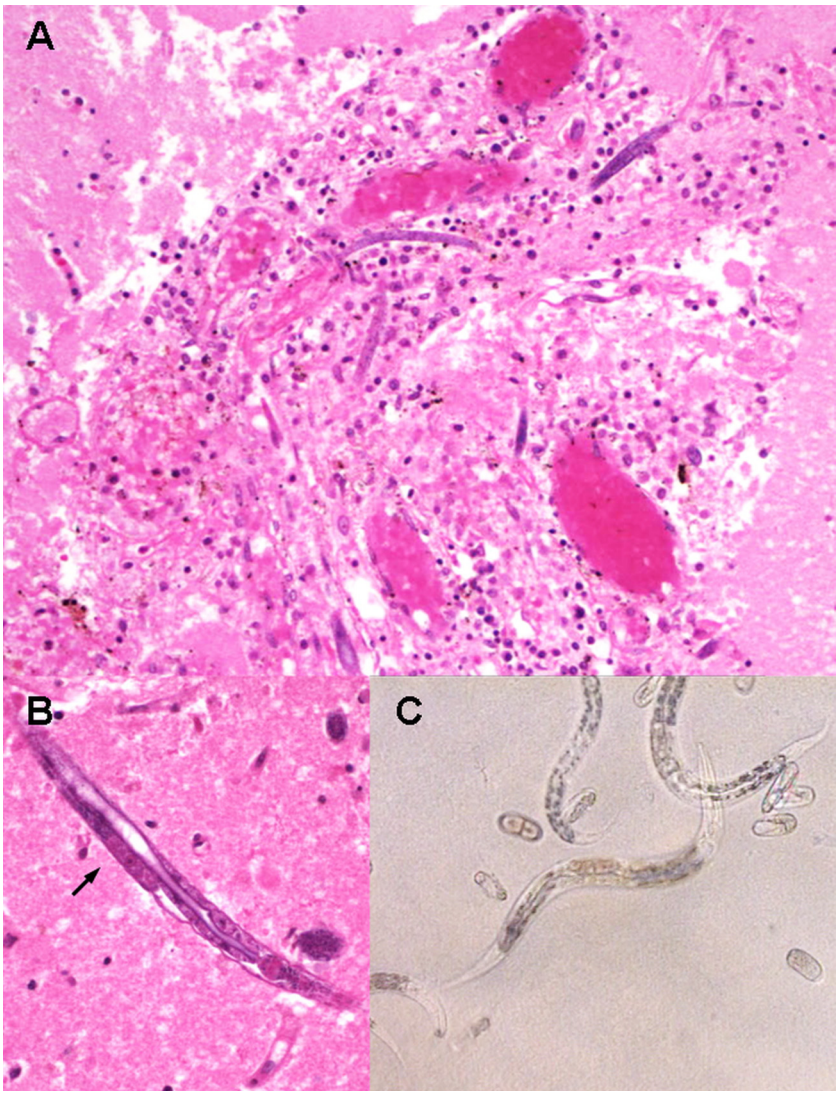

FIG 2 (A) Hematoxylin and eosin (H&E) stain of brain tissue (under ×100 magnification) demonstrates perivascular inflammation with predominant macrophages and lymphocytes surrounding *H. gingivalis* larvae. (B) Third-stage larvae stained with H&E under ×400 magnification show presence of premature genital primordium (black arrow) and bulb of esophagus (at right end of nematode). (C) Microscopy examination of agar plate culture (×400 magnification) shows *H. gingivalis* larvae and eggs in various stages of development.

the environment, *H. gingivalis* has been isolated from horse manure and compost (36). This organism has been reported from all inhabited continents except Australia (37), and isolates recovered from geographically distant localities appear to be genetically similar (6). In the present case, the affected woman had not traveled overseas or had contact with horses in the year prior to her presentation. Infection was likely acquired locally, but this cannot be confirmed as the epidemiology of *H. gingivalis* in Australia is unknown, and there is no published Australian case to date.

The present case is the sixth infection of a human by a *Halicephalobus* sp. described in the literature since 1975 (Table 1). Previously published human cases have all involved immunocompetent individuals in North America. All cases were fatal, with granulomatous encephalitis, suggestive of high neurotropism during infection. Diagnoses were made postmortem, and no anthelmintic treatment had been given. CSFs were obtained antemortem in three cases, white cells ranged from neutrophil to lymphocyte predominance, and pleocytosis with raised eosinophil levels was seen. Granulomatous inflammation was not seen in the current case, possibly due to the use of etanercept, a tumor necrosis factor-alpha (TNF-α) inhibitor, combined with methotrexate (38).

To date, 27 other cases of infection in animals have been described, mainly in horses, with 4 survivors (18, 25, 26, 29). *Micronema deletrix* was used as a synonym for this species in the 20th century. One horse with brain granulomata survived following aggressive debulking surgery complemented by ivermectin treatment (25). Transmission through a manure-contaminated wound had been proposed as the route of infection for one case but was not proven by autopsy (8). To date, human cases have not shed light on the route of transmission. In the present case, histopathological examinations of other organs did not indicate any dissemination of the nematode beyond the central nervous system (CNS). In animals, *H. gingivalis* had been linked to oromaxillary

TABLE 1 Reported cases of *H. gingivalis* infections in humans between 1975 and 2014[a]

Yr	Demographics	Country	Clinical presentation	Premortem CSF findings	Identification of organism	Anthelmintic	Outcome	Reference
1975	Human, 5-year-old male, immunocompetent	Canada	Meningoencephalitis 8 days after fall into manure spreader with facial & mandible injuries	CSF—lymphocytic pleocytosis; 300 cells, 50% lymphocytes, 50% macrophages	Autopsy; morphological diagnosis; spinal cord involvement	No	Death	8
1979	Human, 47-year-old male, immunocompetent	United States	Meningoencephalitis, brainstem signs	Not available	Autopsy; morphological diagnosis; brainstem involvement	No	Death	9
1981	Human, 54-year-old male, heavy alcohol use	United States	Decubitus ulcers over buttock, bilateral internuclear ophthalmoplegia, normal brain scan	CSF—lymphocytic pleocytosis	Autopsy; morphological diagnosis; brain, heart, liver, kidney involvement	No	Death	10
2010	Human, 39-year-old female, immunocompetent	United States	Meningoencephalitis; initial MRI & lumbar puncture normal, improved temporarily with cyclophosphamide + prednisolone; repeat MRI—bilateral ring enhancing lesions	CSF—lymphocytic pleocytosis	Autopsy; morphological diagnosis; brain involvement	No	Death	11
2013	Human, 65-year-old female, immunocompetent	United States	Blurring of vision, encephalopathy, fever, MRI unremarkable	CSF—PMN pleocytosis; 160 leukocytes, 35% macrophages, 27% eosinophils, 14% neutrophils, 20% lymphocytes	Autopsy; morphological diagnosis; brain involvement only	No	Death	12
2014	Human, 74-year-old female, immunosuppressed	Australia	Meningoencephalitis with brainstem signs, MRI frontoparietal meningitis	CSF—pleocytosis; 2,500 neutrophils, 34 mononuclear cells	Autopsy; morphological diagnosis confirmed with LSU rDNA PCR and sequencing	No	Death	

[a] CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PMN, polymorphonuclear leukocytes; LSU rDNA, large subunit ribosomal DNA.

TABLE 2 Reported cases of *H. gingivalis* infections in animals between 1987 and 2014

Yr	Clinical detail	Country	Presentation	Laboratory diagnosis	Treatment	Outcome	Reference
1987	Horse	United Kingdom	Encephalitis	Autopsy; morphological diagnosis	No	Death	13
1990	Two horses	United States	Disseminated infection, lung infection, encephalitis, spinal cord lesions	Autopsy; morphological diagnosis	No	Death	14
1992	Horse	Scotland	Disseminated infection with encephalitis and renal abscess	Autopsy; morphological diagnosis	No	Death	15
1993	Horse	United States	Mandible osteomyelitis renal abscess encephalitis	Prospective; morphological diagnosis	Ivermectin followed with fenbendazole; deterioration on therapy	Death	16
1993	Horse	United States	Maxillary sinus abscess encephalitis	Prospective; morphological diagnosis	Fenbendazole for maxillary sinus infection; deterioration on therapy	Death	17
1993	Horse	United States	Posthitis	Prospective; morphological diagnosis	Ivermectin and diethylcarbamazine	Survival	18
1995	Horse	United States	Encephalitis	Autopsy; morphological diagnosis	Fenbendazole, dimethyl sulfoxide, dexamethasone, and butazolidine	Death	19
1998	Horse	Germany	Osteomyelitis gingivitis	Morphology	Unspecified	Unknown	20
2000	Two horses	United States	Encephalitis uveitis nephritis	Retrospective; morphology	Ivermectin	Death	21
2000	Zebra	United States	Ocular infection	Prospective; morphology	Ivermectin	Death	22
2000	Horse	Canada	Encephalitis	Autopsy; morphological diagnosis	No	Death	7
2001	Horse	United States	Encephalitis	Autopsy; morphological diagnosis	No	Death	23
2001	Horse	United States	Encephalitis	Autopsy; morphological diagnosis	No	Death	24
2001	Horse	Canada	Encephalitis	Prospective; morphological diagnosis	Ivermectin + surgical debulking of granulomas	Survival	25
2004	Donkey	United States	Renal abscess	Prospective; morphological diagnosis	Ivermectin	Survival	26
2006	Horse	United States	Encephalitis	Autopsy; morphological diagnosis	No	Death	27
2007	Horse	Japan	Encephalitis	LSU rDNA[a] PCR and sequencing	No	Death	28
2007	Horse	Switzerland	Posthitis	Prospective; morphological diagnosis	Prednisolone + topical moxidectin + oral moxidectin for 5 mo	Survival	29
2008	Horse	Canada	Mandibular abscess encephalitis	Prospective; morphological diagnosis	Progression on ivermectin, changed to thiabendazole	Death	30
2011	Horse	United Kingdom	Encephalitis	Autopsy; morphological diagnosis	No	Death	31
2011	Horse	Canada	Encephalitis	Autopsy; morphological diagnosis	No	Death	32
2012	Two horses	Iceland	Encephalitis	Autopsy; morphological diagnosis	No	Death	33
2012	Horse	Italy	Encephalitis	Autopsy; morphological diagnosis	No	Death	34
2014	Horse	South Korea	Encephalitis	LSU rDNA[a] PCR and sequencing	Unspecified anthelminthics	Death	35

[a] LSU rDNA, large subunit ribosomal DNA.

infections and posthitis, suggestive of initial mucosal exposure to the invasive larvae, followed by dissemination (17, 18, 20, 29, 30). Exposure through the oromaxillary route may explain the common neurological involvement.

All human cases of *H. gingivalis* infections reported to date were diagnosed at autopsy, despite antemortem suspicions of parasitic infection in some cases. Neurological nematodiasis is rare but can involve parasites such as *Angiostrongylus cantonensis*, *Strongyloides stercoralis*, *Toxocara canis*, *Trichinella spiralis*, and *Gnathostoma spinigerum*, typically associated with CSF and peripheral eosinophilia (39–46). During *H. gingivalis* infection, CSF may initially show only moderate pleocytosis and eosinophilia may be absent (10, 11) and larvae are usually not found in CSF obtained by lumbar puncture. To our knowledge, there is currently no immunoassay or PCR readily available for *H. gingivalis* to provide a timely diagnosis. The D2 and D3 domains of LSU rDNA might be suitable targets for development of a real-time diagnostic PCR (6). The preliminary diagnosis of *H. gingivalis* can be made from nematodes obtained at autopsy since (i) the eggs are distinctive being thin shelled, elongate, and oval at various stages of development, including mature larvae, and (ii) although the larvae have a rhabditiform esophagus and superficially resemble the rhabditiform larvae of *S. stercoralis*, *H. gingivalis* has two esophageal bulbs whereas *S. stercoralis* has one, and the esophageal neck and buccal capsule are longer in *H. gingivalis*. In addition, only filariform larvae of *S. stercoralis*, which have a cylindrical esophagus and a notched tail, have been found in the CNS in disseminated strongyloidiasis (47) and (iii) if adult nematodes are found, they are female only with distinctive morphology.

Treatment responses can be assessed only from previous cases in animals, as none of the human cases, including this case, received anthelmintics. Most affected animals deteriorated (16, 17, 19, 21, 22, 30) despite treatment, and the presence of live worms at autopsy suggests that the anthelmintic treatment was ineffective. *In vitro* susceptibility testing using microagar larval developmental tests (MALDTs) has been used to assess the effects of thiabendazole and ivermectin on the hatching rate and larval development of *H. gingivalis* (48). Thiabendazole at concentrations of 10 to 100 μg/ml showed a dose-dependent inhibition effect on the hatchability of eggs. However, no inhibition of larval development was observed. Thus, *H. gingivalis* appears to have some intrinsic tolerance of ivermectin, but larval development can be temporarily suppressed at 2 μg/ml. Reversal of inhibition can be seen, despite incubation with ivermectin for 72 h. Pharmacokinetic studies have showed that ivermectin rarely enters the CNS since it is actively removed by the P-glycoprotein, an abundant transporter protein in the brain. This can result in an undetectable CSF level, despite a parenteral dose of 200 μg/kg of body weight, which is often used for disseminated *S. stercoralis* infection (49). If high parenteral doses do allow ivermectin to penetrate the CNS, adverse CNS effects, including decreased consciousness, may occur (50). There is a paucity of pharmacokinetic data on cerebral penetration of thiabendazole. Using thiabendazole at 23 mg/kg every 12 h, one study has shown that the highest drug level detectable in CSF from an individual with cerebral strongyloidiasis was only 1.8 μg/ml (51), significantly below the concentration required for *H. gingivalis* egg inhibition. The benefit of adjunctive corticosteroid is also questionable due to paucity of evidence and lack of clinical improvement (52).

To date, all reported cases of human *H. gingivalis* infection have led to fatal meningoencephalitis, and diagnoses were made at autopsy. Brain biopsy should be considered for indeterminate cases of meningoencephalitis (53). Antemortem diagnosis remains a major challenge, as there is no laboratory test with a reasonable turnaround time, and routine CSF findings and radiologic features are nonspecific. Nonetheless, PCR-based sequencing of DNA from brain biopsy material and CSF could potentially assist in diagnosis. Treatment has not been described in human cases, but pharmacokinetic studies (48, 49) suggest that treatment with ivermectin or thiabendazole administered parenterally may not be effective because of poor killing effect *per se* and inability to achieve therapeutic levels in CNS.

Nucleotide sequence accession number. The sequences determined in this work were deposited in GenBank under accession no. KP307928.

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