

Horse anaplasmosis as a cause of CNS infections and the use of computed tomography as a diagnostic imaging tool to present of its cerebral form: literature review supplemented with a clinical case

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Summary

Anaplasma phagocytophilum is an intracellular bacteria that causes several non-specific symptoms (for instance, horse lying down), posing problems in differential diagnosis. Usually, symptoms appear few days after tick exposure. Less often their neurological forms are observed to be correlated with visible neuroanatomical localization, with computed tomography (CT) or magnetic resonance (MRI). The aim of this paper is to present the review of a neurological form of EGA in a horse as well as localization of hypodense cerebral changes with the use of CT. This work also describes a case of a horse suffering from anaplasmosis confirmed by positive PCR results for *Anaplasma phagocytophilum* from peripheral blood and cerebrospinal fluid, four months after exposure to ticks. In 30% of such cases blood smear tests showed no evidence of bacteria. Hypodense lesions were observed in the CT scan of the brain and brainstem. As demonstrated by literature in humans, anaplasmosis can be considered in differential diagnosis as a potential cause of non-specific neurological symptoms, particularly in areas endemic for anaplasmosis, where animals are exposed to contact with ticks. Possible neurological complications in horses as a result of anaplasmosis have been reported but there are no reports on the identification and diagnosis of the brain in cerebral anaplasmosis by using CT or MRI imaging tools. So far, such a diagnostic procedure in the case of tick diseases has been identified in case of humans only.

Keywords: anaplasmosis, horse, neurological symptoms, CT scan

Changes in the natural and social environment brought about by climate change have created good conditions for the extension of the tick's spatial and temporal distribution (14, 40). In Europe, *Ixodes ricinus* is the main vector of *Anaplasma phagocytophilum* (1, 25, 40, 44). *A. phagocytophilum* is a gram-negative, pleomorphic, intercellular bacteria forming macrocolonies (morulae) in infected granulocytes. It is a causative agent of equine granulocytic anaplasmosis (EGA). The severity of an EGA infection is influenced by several factors, including the strain of *A. phagocytophilum*, possible co-infections, patient age, immunological status of the infected animal, and factors such as climate and

management (10, 39). The incubation period of EGA is approximately 10 days. The course of equine granulocytic anaplasmosis may be sub-clinical or acute (7, 8, 10, 29). Pyrexia, anorexia, limb oedema, icterus, petechiae, reluctance to move, and ataxia are typical clinical signs of EGA, whereas rare symptoms include recumbency (29) or rhabdomyolysis (18), cavitory effusion (33), and presumptive tick paralysis (22). Additionally, in experimentally infected horses transient systolic heart murmur has been reported (11).

A. phagocytophilum appears to be a rare agent in CNS infections (5, 45), which has nonetheless been observed in medical reports (16, 19, 31, 44). Severe neurologi-

cal symptoms in EGA have been previously reported (37) but never in Poland. Neurological disorders in the course of infection are also uncommon in humans (19, 20, 27, 34), sheep, cattle (39), dogs (7) and cats (1, 5, 36, 39, 41).

In human medicine, meningoencephalitis has been reported only in about 1% of cases, although the cause of neurologic dysfunction in granulocytic anaplasmosis is yet to be explained (11, 20, 27, 43). However, a number of differential system manifestations have been described, including brachial plexopathy, cranial nerve palsies, demyelinating polyneuropathy and bilateral fascial nerve palsy (16, 19, 23, 37). In case of humans suffering from HGA, neurological symptoms in the brainstem from cerebral infarction have been reported. Computed tomography (CT) shall be considered then, as a useful and appropriate tool to understand the cerebral lesions (16, 23, 35, 37).

The aim of this paper is to present the case of cerebral EGA in a horse as well as localization of comorbid hypodense cerebral changes with the use of CT.

Material and methods

The material for this study was based on the available literature on neurological complications after contracting anaplasmosis by humans and animals. Horses with neurological symptoms: non-specific swellings, atactic gait or cerebral symptoms such as strabismus, recumbency, paralysis, stupor, nystagmus are also described (6, 15, 42).

The study is also based on a clinical case of a 12-year-old mare with an open wound on the front limb at the metacarpal region that was admitted at the Surgery Clinic of Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland, in which a case of chronic cerebral anaplasmosis was diagnosed.

In the literature available, in case of horses the use of radiological imaging tools (CT, MRI) was not reported in respect of the above symptoms to locate changes in the cerebral area (35). In humans, after localization with the use of imaging diagnostics, a biopsy from the changed cerebral area may be performed (12, 35).

The changes can also be seen posthumously, macroscopically, which may indicate an advanced and intense chronic inflammatory process (Fig. 1); the pathomechanism, however, is unknown.

The basic test for anaplasmosis is the blood smear test which, however, gives a reliable result only in 30% of infected patients (2, 3). PCR performed from peripheral blood and cerebrospinal fluid (CSF) could be considered the gold standard. In the case of our mare, both tests were performed and the whole blood and CSF were taken from the horse for molecular tests (PCR) for herpesvirus, borreliosis and anaplasmosis. Other diseases, such as herpesvirus and borreliosis, should be excluded. Anaplasmosis was found in the studied mare by examining the blood and the cerebrospinal fluid but the DNA of *A. phagocytophilum* was found in the blood and CSF. The sequence of the obtained PCR product (247 bp) was: GGCGGTTCCGTAAGTTAAAGGTGAAATGCCAGGGCTTAACCTG-GAGCTGCTTTTAATACTGCCAGACTAGAGTCC-

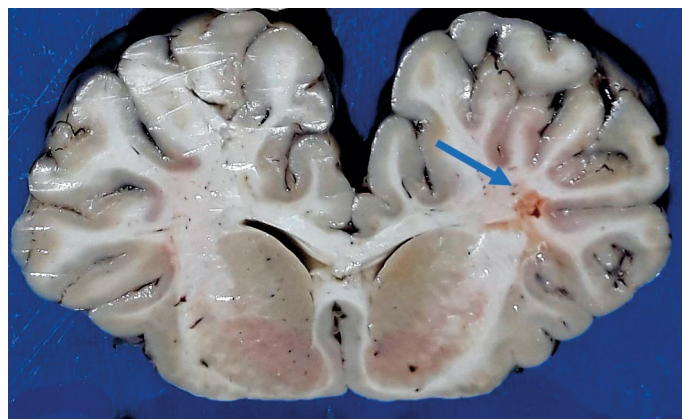


Fig. 1. Macroscopic images of the brain of a horse with anaplasmosis. Parasagittal section show areas (plaques) of demyelination in white matter of the brain. Probably it is a brain specimen of ischemic infarct

GGGAGAGGATAGCG-GAATTCCTAGTGTAGAGGT-GAAATTCGTAGATATTAGGAGGAACACCAG-TGG-CGAAGGCGGCTATCTGGTCCGGTACTGACGCT-GAGGTGCGAAAGCGTGGG-GAGCAAACAGGATTA-GATACCCTGGTAGTCCACGCTGTAAACGATGAGTGCCTAA and showed 100% homology with the sequence of the 16S RNA *A. phagocytophilum* gene fragment, deposited in the gene bank (GU183908).

Results and discussion

So far in Poland, clinical cases of granulocytic anaplasmosis in horses have been diagnosed (2, 3, 8, 24), but never its chronic form involving neurological symptoms after several-months' tick exposure. This case is an example of the rare chronic, neurological form of *Anaplasma phagocytophilum* infection in a horse. In other countries, acute cases of horses' neurological disorders have been reported (15, 22, 42).

It is believed that after the tick bite, the bacterium infiltrates the blood and the lymphatic system, triggering a pathological inflammatory cascade that may damage internal organs (4, 27, 34). In cases of equine and human anaplasmosis, the neutrophils carrying the *A. phagocytophilum* pathogen circulate in the organism, probably to a greater extent than in the peripheral tissue (4, 9, 17). This may be of key significance relative to the causes of pathological lesions observed in the course of such infections. The neutrophils are involved in the inflammatory process. *In vitro* studies have also demonstrated that the bacterium inhibits the release of TNF-alpha, interleukin 6 and 13 (IL-6, IL-13) in the bone marrow mononuclear cells (BMMC) cell lines (13, 26, 30, 32).

In terms of the organ dysfunctions accompanying *A. phagocytophilum*, there have been reports evidencing hematological and biochemical disorders (7, 13, 41). Elevated levels of hepatic enzymes and hyperbilirubinemia, for example, may occur, both of which were observed in the described horse.

In humans suffering from HGA, the above factors may constitute evidence of immunosuppression. *A. phagocytophilum* has the ability to inhibit the patient's defense

mechanisms while being poorly immunogenic itself, mainly due to the absence of lipopolisacharyd and peptidoglycan in its cellular wall (13, 31).

A. phagocytophilum may also target hematopoietic and lymphoreticular cells. The pathogen in question has unique pathogenic properties and shows tropism relative to the cells of the hematopoietic and phagocytic systems. Replication takes place in the phagocytic vacuoles. Intensified cytolytic activity has been observed, but it remains unclear whether *Anaplasma* directly damages cells. This probably implies the accumulation of inflammatory cells and a systemic initiation of proinflammatory response (26, 30). *A. phagocytophilum* infects endothelial and myeloid precursor cells (9, 20), human dermal cells and mast cells originating from the bone marrow, by attacking dermal mast cells in the location of the tick bite (13, 32). Symptoms include inflammation of the small arteries and veins associated with the subcutaneous fascia and distal limb nerves (4, 13). As mentioned above, *A. phagocytophilum* spreads throughout the organism via the blood and lymphatic vessels, which leads to bone marrow damage and pancytopenia, especially thrombocytopenia. The exact mechanisms responsible for the decreased platelets count in the course of the infection have yet to be discovered (13). It is believed that thrombocytopenia results from the destruction of thrombocytes by cells of the immune systems, their increased phagocytosis by macrophages and intensified breakdown in the spleen (30, 32, 41). In horses experimentally infected with *A. phagocytophilum* the autopsies revealed hemorrhages in the internal organs, kidney thrombosis and vessel inflammation (11). However, the literature does not report any consistent results evidencing a clear correlation in terms of pathological lesions in the heart, brain, kidney and skeletal muscle tissues in severe and chronic cases of anaplasmosis (11, 30, 32).

The course of granulocytic anaplasmosis in mammals can be subclinical or acute (11, 20). It should be noted that while characteristic changes in the blood are pathognomonic in the acute form of anaplasmosis, they tend to be considerably less pronounced in the chronic/subacute form. In the treated patient, alimentary tract disorders may have led to an increase in serum hepatic enzyme activity. Increased concentrations of urea were also observed in the serum of sick animals, likely due to dehydration (6).

Many infections caused by *A. phagocytophilum* probably remain undiagnosed. Subclinical infections are common while the diversity of the symptoms, including clinical ones, is not pathognomonic (21, 24). The observed symptoms may range from mild fever to potentially life-threatening complications, a factor which hinders early diagnosis, particularly in animals. Clinical neurological symptoms that may derive from the CNS pathologies are not commonly reported in horses suffering from anaplasmosis.

CT scans may help to verify brain lesions in the context of clinical neurological symptoms (16, 23, 35, 43).

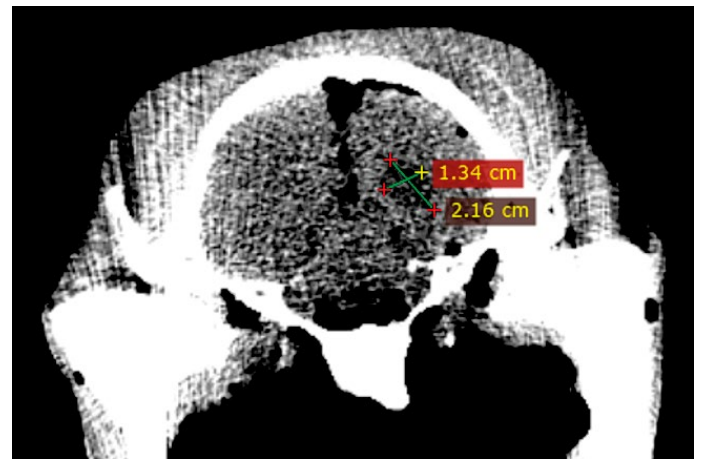


Fig. 2. A non-contrast CT scan in coronal view showing a hypodense lesion in the region of left basal ganglia, which most likely corresponds to a subacute/chronic ischemic change

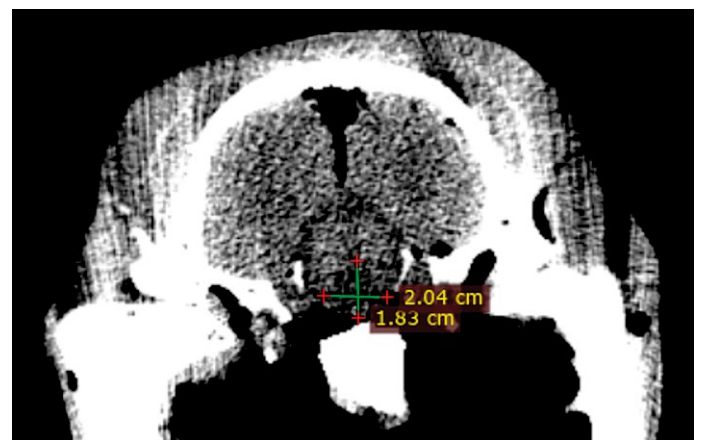


Fig. 3. A non-contrast CT scan in coronal view showing a hypodense lesion in the brainstem, which most likely corresponds to a subacute/chronic ischemic change

They facilitate a better understanding of the mechanisms of cerebral ischemia. On the postmortem CT scan, we found two hypodense lesions, one in the deep grey matter around the left lateral ventricle, and the other in the brain stem in the ventral region (Figs. 2, 3). They most likely correspond to subacute/chronic ischemic lesions resulting from the inflammatory angiopathy caused by the *Anaplasma* infection. The clinical symptoms, especially loss of consciousness, strabismus, nystagmus and tachypnea, correlate with the changes located in the brainstem. The literature includes one article which reported lesions caused by an *Anaplasma* infection located in the region of the basal ganglia in a human patient (37, 43).

Cerebral infarction may occur due to a severe narrowing or obstruction of the cerebral arteries, causing ischemia and depriving the brain tissue of sufficient access to glucose, oxygen and lipids, which may lead to necrosis (28).

In the described case of a mare suffering from EGA, due to the likely chronic course of anaplasmosis lasting a number of months, numerous microinfarctions may have occurred in the brain. Cerebral microinfarctions are small lesions typically considered to be ischemic. Patients may in fact suffer from hundreds to even

thousands of cerebral microinfarctions that considerably disturb structural cerebral connections (28). In its last month, the described mare suffered from intensified gait disorders and recumbency, which may have resulted from the coexistence of the anaplasmosis and microinfarctions (12).

In a study on middle cerebral artery occlusion in Wistar rats, in isolated infarction locations only a small number of neurons with signs of necrosis were observed in the first 4 hours. The earliest significant increase in the percentage of necrotic neurons (15%) in the region of the obstructed artery was reported only after 6 hours. The results correlate with reports concerning the progress of neuronal necrosis after permanent closure of an artery. The reasons for the progression of the lesions are unknown. It remains to be determined whether the extent of the neurological deficit caused by arterial closure correlates with the number of necrotic neurons. It has been confirmed that cerebral microinfarctions can continue for up to several weeks. A microinfarction causes functional hemodynamic deficits and neuronal defects in the surrounding tissue. Neuronal function is impaired in the cortical regions, at least 12 times larger than the size of the stem lesion itself. Patients may show functional disorders (12, 28).

Computed tomography is not the modality of choice for assessing microinfarcts. This type of lesion can be detected by using MRI, especially in T2-weighted and FLAIR sequences.

The samples for histopathology were taken from the medulla oblongata and the temporal part of the cortex. Microscopic examinations of the gray matter revealed microfoci of perivascular necrosis, signs of neuronal vacuolization, degeneration, necrosis and loss. Focal axonal necrosis and spherulosis were noted within the gray matter (Figs. 4, 5). Reactive proliferation of the microglia close to the degenerative neurons was noted. There were signs of intensive spongiosis within the medulla oblongata, inadequate to the age of the animal (Fig. 6).

The determination of the actual correlation between anaplasmosis and cerebral infarction requires further research. It should also be determined whether cerebral infarctions can result from thrombosis caused by damage to endothelial cells, which may be hypothetically triggered by *A. phagocytophilum*, or as in other cases of rickettsia, by platelet diffusion (16, 22).

Given the growing incidence of tick-borne diseases, both in humans and animals (11, 38, 40, 44) living in endemic regions for anaplasmosis, in cases with coexisting neurological disorders potentially related to CNS, *A. phagocytophilum* ought to be considered as a possible cause of clinical symptoms in the course of differential diagnostics. The most pressing challenge currently relates primarily to the ability to quickly diagnose an infection caused by *A. phagocytophilum* given the non-specificity of its clinical symptoms and the intracellular character of the pathogen (16, 23).

Computed tomography has served as a useful tool for assessing changes in the brain. Hypodense changes

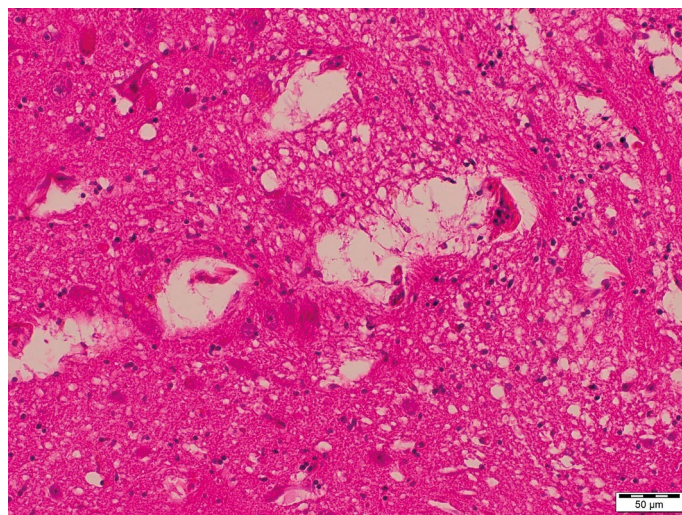


Fig. 4. Microfocal perivascular necrosis, signs of neuronal vacuolisation, degeneration, necrosis and loss. Axonal necrosis and spherulosis (H + E)

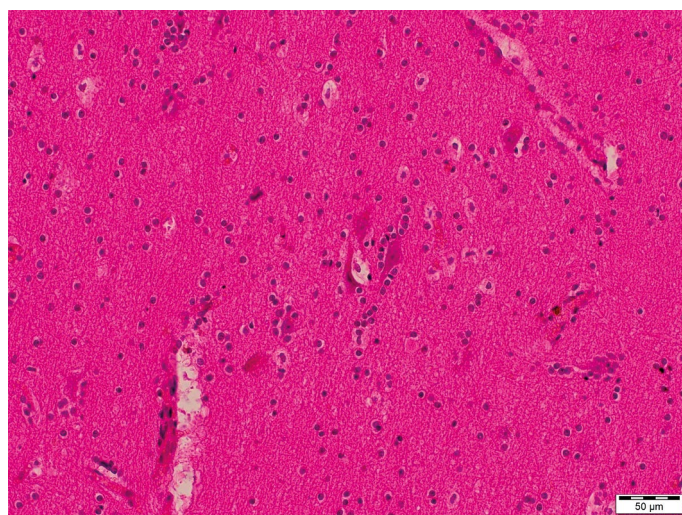


Fig. 5. Reactive proliferation of microglia close to degenerative neurons within gray matter (H + E)

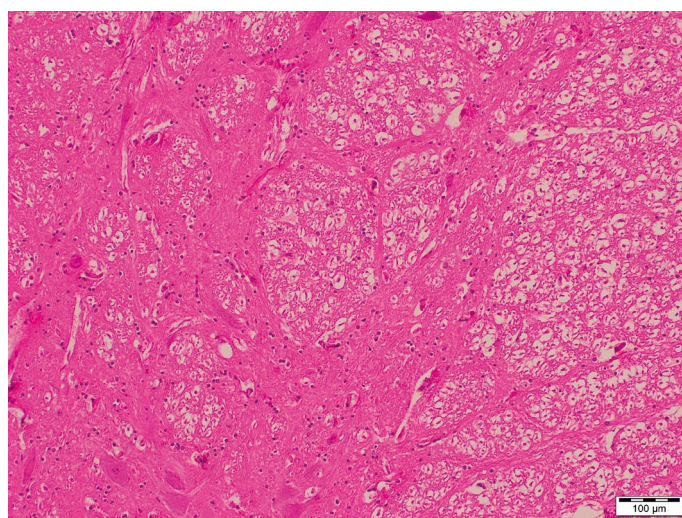


Fig. 6. Intensive spongiosis within the medulla oblongata (H + E)

in brain computed tomography correlated with the neurological clinical signs of the animal. To date, this form of anaplasmosis in radiological terms has been described (only) in humans. Due to non-specific clini-

cal neurological symptoms, patients were referred for CT or MRI scans. The diagnosis of such cases, both in humans and animals, causes many difficulties (in the case of treating horses, especially those who work in the field). Perhaps the article could serve as an example to consider anaplasmosis in the differential diagnosis as a potential cause of the disease, especially in endemic areas, even several months after the animal's exposure to ticks in the case of nonspecific, complex neurological symptoms. The article may also draw attention to the need to examine the CNS area in the case of confirmed anaplasmosis in order to explore the pathomechanism of changes visible in the radiological image. This highlights the importance of imaging to explain the nature of the observed neurological deficits in animals.

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