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TITLE OF CASE ***Do not include "a case report"***
CLINICAL AND MRI FINDINGS IN TWO UNRELATED CATS WITH GLOBOID CELL LEUKODYSTROPHY
SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

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Two unrelated male cats, both five-month-old, were referred for progressive neurological signs characterized by intentional tremors, paraplegia with absence of nociception in the pelvic limbs, weakness, dysmetria with reduced flexor reflex on thoracic limbs and bilaterally reduced menace response. Magnetic resonance imaging, performed by a 0,25T EsaoteVet Grande, showed diffuse and irregular intramedullary T2-weighted hyperintensity between T3 and L3; these lesions were isointense on T1-weighted images without contrast uptake. In one patient MRI of the brain was obtained and mild cerebellar volume reduction was found. Histological examination of the brain and spinal cord demonstrated myelin loss and perivascular accumulation of PAS positive big macrophages and these findings were consistent with Globoid Cell Leukodistrophy, as previously described in cats. Although not specific, in young cats with progressive spinal neurological signs, especially when associated with cerebellar signs, and irregular but diffuse T2 intramedullary hyperintensity, T1 isointensity without contrast uptake, Globoid Cell Leukodystrophy should be suspected.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Globoid Cell Leucodystrophy (GLD) or Krabbe disease is a rare fatal lysosomal storage disease. Lysosomal storage diseases are inherited abnormalities due to intracellular accumulation of results of defective metabolic pathway (1). GLD belongs to the group of sphingolipidosis and it is due to an autosomal recessive disorder, secondary to the deficiency of the enzyme galactocerebrosidase (GALC) (2). This enzyme, also termed galactosylceramidase, is involved in the degradation of the myelin turn over products, especially of the psychosine and galactosylceramide, which accumulate within oligodendrocytes, myelinating the Central Nervous System (CNS) neurons, and Schwann cells around nerves, causing cell death (3) and eliciting an inflammatory response. As result, myelin production and maintenance cease (4) and there is astrocyte reaction (astrocytosis) and perivascular infiltration of globoid and sometimes multinucleated macrophages (5, 6). These unique cells are the so-called Globoid Cells because of their appearance due to the intracellular accumulation of the PAS-positive material referable to galactosylceramide.

The disease has been reported in humans (7-10), monkeys (*Macaca Mulatta)* (11), mouse (12), sheep (13, 15), dog (16-23) and cat (2, 5, 24, 25).

In cats, onset of clinical signs is between five weeks and four months of age and is typically characterized by progressive paraparesis or tetraparesis evolving to paraplegia, weakness, and focal or generalised tremors, sometimes accompanied by segmental spinal reflex loss and other central nervous system signs (2, 5, 24, 25).

The clinical signs are the result of the demyelination of cerebellum, white matter of the cerebrum, spinal cord and nerves.

Magnetic resonance imaging (MRI) findings are described in dogs (3, 22, 23) where also genetic test is available (18).

The aim of this report is to describe the neurological symptoms and the MRI findings in two unrelated cats with histologically confirmed Globoid Cell Leukodystrophy.

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CASE PRESENTATION ***Presenting features, clinical and environmental history***

Two unrelated neutered male cats, both five-months-old, were referred for slowly progressive neurological signs, which followed mild gastroenteric signs and hyperthermia (40 °C). Case 1, a rescue patient in whom the onset and the progression of clinical signs were unknown, showed paralysis with absence of nociception in pelvic limbs and weakness-dysmetria with reduced flexor reflex on thoracic limbs. Case 2 had a three weeks history of paresis, ataxia and bilateral reduction of postural reactions on pelvic limbs progressively evolving to paraplegia. Both patients showed intentional head and truncal tremor although mild in Case 2, bilateral menace response decrease and were previously treated with clindamycin (12-25 mg/kg BID), with no improvement. Neuroanatomical localization was suggestive of multifocal lesions with cerebellar and spinal cord involvement mainly at the thoracolumbar (T3-L3) area but also with possible minor caudo-cervical (C6-T2) involvement. Differential diagnosis included inflammatory-infectious and degenerative diseases while a multifocal neoplasia, such as lymphoma, was considered less likely due to the young age.

INVESTIGATIONS ***If relevant***

Complete cell blood count, serum biochemistry, thoracic and vertebral column radiographs were unremarkable in both cats; both patients were seronegative for feline leukaemia and feline immunodeficiency viruses.

Magnetic resonance imaging (MRI) of the thoracolumbar spine were performed with a 0,25T-unit and included FSE T2 and T1 WI on sagittal and transverse planes; T1WI were repeated after intravenous paramagnetic contrast medium administration (0.1 mmol/kg gadolinium, Magnevist Bayer ®). Both cats showed diffuse and irregular intramedullary T2-WI hyperintensity mostly between T3 and L3 vertebrea; no obvious morphological and signal changes were detected on pre and post-contrast T1WI. MRI of the brain and neck was also obtained in Case 1 and moderate cerebellar volume reduction was found, as indicated by widened cerebellar sulci and fourth ventricle (Fig 1). Based on MRI changes an inflammatory disease, either immune-mediated or infectious, was deemed most likely and then cerebrospinal fluid was collected from the lumbar cistern.

Cerebrospinal fluid analysis in Case 1 showed 2 white blood cells (WBC)/microl and a protein level of 62 mg/dl, and in Case 2 13 WBC/microl and protein level 300mg/dl (reference ranges: WBC count <5 cell/microl and protein concentration < 45mg/dl); WBC were represented by lymphocytes and monocytes. Those findings were mostly compatible with an albumino-cytological dissociation and mild pleocytosis in Case 2 that, despite being often non-specific, could be suggestive of a degenerative nervous system disease.

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DIFFERENTIAL DIAGNOSIS ***If relevant***
Differential diagnosis included inflammatory-infectious and degenerative diseases while a multifocal neoplasia, such as lymphoma, was considered less likely due to the young age.

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TREATMENT ***If relevant***

A primary inflammatory disease at this stage seemed less likely. However, a therapeutic attempt with prednisolone (0.5 mg/kg BID) and clindamycin (15mg/kg BID) was made.

OUTCOME AND FOLLOW-UP

Patient 1 died naturally two days after the MRI for unknown causes; in Case 2 the steroids were discontinued approximately in two weeks and clindamycin after four weeks, due to the lack of improvement. Case 2 was euthanased one year after the first neurological examination due to the dramatic progression of the neurological signs. The brain and the thoracolumbar spinal cord were collected and then submitted for histology in both cases.

On post-mortem examination no gross changes were observed. The entire central nervous system was fixed in phosphate buffered 4% formalin solution. Tissue samples were processed by routine methods for histology and sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), Luxol fast blue, and toluidine blue. Selected brain sections were immunolabeled by the peroxidase-anti-peroxidase method with a polyclonal antibody against glial fibrillary acidic protein (GFAP; DakoCytomation, Glostrup, Denmark) diluted 1 in 100.

Histological lesions in both cases were characterized by bilateral and symmetrical myelin loss and dystrophy throughout the neuraxis. The most severely affected regions of the brain were the corona radiata, corpus callosum, optic tracts, optic radiation, fimbria, fornix, inferior cerebellar peduncles, and subcortical white matter of the cerebellum. Similar white matter changes were also found throughout the thoracolumbar spinal cord. Lesions consisted in conspicuous perivascular aggregates of large, rounded macrophages (i.e. globoid cells), associated with diffuse loss of myelin and astrogliosis (Fig. 2). Globoid cells had abundant cytoplasm, which was faintly eosinophilic, strongly PAS positive, and non-metachromatic. Nuclei were oval with indented nuclei membrane and dense chromatin. The globoid cells were also frequently multinucleated with eccentric and flattened nuclei. In the most severely affected areas, occasional foci of malacia were detected. Infiltration of globoid cells was also observed in the cranial and spinal nerve roots accompanied by fiber nerve loss. The leucodystrophic process was accompanied by extensive astrocyte reaction with presence of numerous GFAP-immunolabeled gemistocytic astrocytes. Sparing of some white matter structures, including arcuate subcortical fibers, internal and external capsule, anterior and posterior commissure, alveus, cerebral peduncles, superior and middle cerebellar peduncles, cerebellar foliae, pyramids, and the fasciculus proprius of the spinal cord was observed. Morphologic and topographic histopathological changes and the histochemical findings were consistent with GLD, as previously described in cats (5).

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DISCUSSION ***Include a very brief review of similar published cases***

Globoid Cell Leukodistrophy is very rare and fatal condition in all the species, including human beings. It has been reported in six cats, three in USA (2, 24), two in Italy (5) and one in Japan (25), albeit only clinical and histopathological features were described. As in our cases, pelvic limb involvement is a predominant feature and inevitably progresses to paraplegia with loss of nociception in all affected patients; tremors of head and trunk were reported only in two of six cats (2, 5) and they were present in both our cases, though milder in case 2, despite the severe cerebellar white matter degeneration. As in other degenerative diseases, there is a mismatch between severity of the histological changes in GLD and severity of the clinical signs; prosencephalic signs vary in fact from mild to absent and so far cognitive impairment was reported in one cat (25), despite wide involvement of the telencephalic white matter.

This is the first report of MRI findings in cats with histopathologically confirmed GLD.

Magnetic resonance imaging changes, even if not specific, are helpful to obtain an ante mortem presumptive diagnosis in association with clinical signs and progression of the disease; moreover, they are especially useful to rule out other causes of CNS disease, potentially more frequent in cats, such as inflammatory/infectious disease. Some of the MRI findings may overlap between degenerative and inflammatory disease (Feline Infective Peritonitis Virus (FIPV) or, to a lesser degree, toxoplasmosis or, finally, non-suppurative meningoencephalitis of unknown etiology, the latter tends to usually show more contrast enhancement; even the distribution of the lesions may help in differentiating the two forms, always in conjunction with the clinical signs, focal vs multifocal localization and their course (26). MRI findings in cats with CNS inflammation, despite not being pathognomonic, are often consistent with multiple hyperintense areas on T2WI and FLAIR images with variable contrast enhancement and mass effect, which were not present in our cases. Especially in FIPV infection their distribution and in particular the involvement of ependymal lining and meninges are key features. CSF abnormalities may also support the possibility of a primary CNS inflammation/infectious (27). CSF analysis was normal in one of our cats and showed a very mild pleocytosis in the second one, possibly secondary to the CNS damage.

In utero Parvovirus infection is one of the first suspicion in young cats with diffuse and symmetrical cerebellar signs and MRI findings characterized by cerebellar volume reduction similar to one of our cases, but no spinal involvement has been described and signs are typically non progressive (1,28-31)

Some degenerative diseases, such as mannosidosis and gangliosidoses, involve the cerebellum (1), but no concurrent spinal involvement has been reported, except for sphingomyelinosis, which is however histologically easily distinguishable from GLD (32).

In dogs, Cozzi et al (3) and Bradbury (22, 23) described MRI pathological changes in a total of five dogs, characterized by T1 hyperintensity of the corpus callosum and bilaterally symmetrical T2 hyperintensity of the corpus callosum, centrum semiovale, internal capsule, corona radiata and cerebellar white matter with contrast enhancement only in one case. Brain atrophy was also detected. In Case 1, no changes of the cerebral white matter were visible on MRI images, even if on histopathological examination it appeared diffusely degenerated. A possible explanation is that the MRI study was performed with a low field unit, while in the

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previous studies in dogs a 1.5T-unit was used; however, other possible reasons include the milder degree of the lesions and/or their smaller size in a smaller brain compared to dogs. A normal brain MRI has also been described in clinically affected human patients, suggesting that the signs may precede the MRI changes (33) or may not be of the same degree of those of the symptoms. Spinal MRI findings in our cats, though not specific for a particular disease, could suggest irregular areas of astrogliosis as demonstrated by the histopathological examination; those microscopic findings also involved to a lesser degree the grey matter.

In our patients, histopathological findings were strongly consistent with those previously described in cats affected by GLD (2, 5, 24, 25), and then confirmed the definitive diagnosis of this rare degenerative disease.

In order to achieve the ante mortem diagnosis, experimental studies were performed on dogs affected by GLD as spontaneous translational disease model, by evaluating the evolution of clinical signs and the pathological changes (3, 20-23, 34). Although alterations in Nerve Conduction Velocity, Brainstem Auditory Evocated Response test (3, 23), CSF psychosine concentration (23), galactosylceramidase activity in peripheral blood leukocytes (14) were described, no convincing or specific results were obtained to definitely achieve the ante mortem diagnosis of GLD. In 1996 the gene mutation responsible of the disease was isolated by Victoria et al (18) in West Highland White and Cairn Terrier and in 2006 in the Irish Setter (19). A genetic test has been devised for West Highland White and Cairn Terrier in order to obtain ante mortem definitive diagnosis. Nevertheless, this test cannot be extended to other breeds and species, where the definitive diagnosis is still reached by post mortem demonstration of the above reported histopathological changes.

In young cats, history of slowly worsening neurological signs characterized by pelvic limbs paresis progressing to paralysis, ascending weakness-dysmetria, head and truncal tremors should be considered as highly suggestive of GLD (5, 24, 25). Moreover, despite MRI changes in GLD are nonspecific, they are useful in ruling out other disease and in association with the clinical signs, their progression and the CSF findings, are helpful in reinforcing the intra vitam suspicion of this degenerative CNS disease.

Globoid Cell Leucodystrophy should be considered as one of the main differential diagnoses in young cats with progressive thoracolumbar spinal cord signs, possibly associated with cerebellar and minor cervical signs, and MRI changes characterized by irregular and diffuse spinal T2 hyperintensity and mild cerebellar atrophy. Nevertheless, histopathological confirmation is still necessary for the definitive diagnosis.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

1) GLD should be considered ad differential diagnosis in in young cats showing slowly worsening neurological signs characterized by pelvic limbs paresis progressing to paralysis, ascending weakness-dysmetria, focal or generalised tremors.

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2) MRI changes, even if nonspecific, are useful in ruling out other disease and in reinforcing the ante mortem suspicion of this degenerative CNS disease.

3) In cats definitive diagnosis is obtained only through histopathology, given the lack of genetic mutations identified.

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