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CASE REPORT

Companion or pet animals

Adult-onset neuronal ceroid lipofuscinosis in a smooth-haired dachshund

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Abstract

A 5-year-old, smooth-haired miniature dachshund exhibited a progressive history of frequent episodes of aggression towards objects, head pressing, circling and intermittent pelvic limb ataxia over a period of 2 weeks. Visual impairment was also noticed several months prior. Neurolocalisation was consistent with forebrain disease. Blood and urine analysis, magnetic resonance imaging of the brain and cerebrospinal fluid analysis were all unremarkable. The patient was euthanased due to disease progression, and postmortem histopathological analysis and electronic microscopy identified the accumulation of intracellular granular material in a number of neurons, mainly located in the thalamus and hypothalamus. This supported a diagnosis of neuronal ceroid lipofuscinosis. Genetic testing showed no mutations in the causative genes reported for this breed. This case reports the occurrence of a potentially novel subtype of neuronal ceroid lipofuscinosis, due to a currently unidentified genetic mutation, leading to an adult onset of clinical signs in the dachshund.

BACKGROUND

Neuronal ceroid lipofuscinoses (NCLs) are a group of progressive neurodegenerative lysosomal storage diseases that affect humans and many breeds of dogs as well as cats, horses, cattle, sheep, mice and monkeys.[1]

NCLs occur naturally, have a hereditary basis, and result from the accumulation of autofluorescent lysosomal storage material in the brain, retina and other non-neuronal cells.[2] As such, NCLs can be classified as a subtype of lysosomal storage disease. Lysosomal storage diseases are caused by disturbances in protein degradation as a result of mutations in genes encoding proteolytic enzymes along a metabolic pathway.[3] This storage process, along with associated effects on cellular metabolism, leads to progressive neuronal loss and degenerative disease.[1,4]

NCLs can be classified by the age of onset, specific identified genetic mutations leading to the disease[5] and the ultrastructure of storage deposits.[4] A variety of NCLs are reported in dogs, with some breeds appearing to have susceptibility to particular genetic mutations.[2,5–14] To date, mutations in the TPP1[6] and PPT1 canine genes[5] have been identified in dachshund dogs, leading to NCL with clinical signs presenting in young dogs (<1 year-old).

NCL with an adult onset of clinical signs is rare, although it is typical in Tibetan terriers with mutations in the ATP12A2 canine gene.[14] NCL with an adult onset of clinical signs has previously been reported in the dachshund breed—in one 3-year-old wire-haired dachshund[15] and two long-haired dachshunds at 5 and 7 years of age.[16]

To the authors' knowledge, this is the first reported case of NCL with an adult onset of clinical signs in a smooth-haired dachshund that does not carry the previously reported genetic mutations in the breed. This case therefore likely represents a newly reported subtype of NCL in a smooth-haired dachshund leading to adult onset of the disease due to a currently unidentified genetic mutation.

CASE PRESENTATION

A 5-year-old, female, neutered, smooth-haired, miniature dachshund presented for neurological evaluation of a few months' history of suspected visual impairment and a 2-week history of increasingly frequent episodes of unprovoked aggression towards inanimate objects (Video 1), head pressing and tendency to circle towards the left. Brief episodes of pelvic limb ataxia were also observed after some of the periods of aggression.

The patient had been imported to the United Kingdom from Poland 4 years before presentation. Apart from the neurological signs, the patient was described as a healthy dog with no other systemic concerns.

VIDEO 1 One of the episodes of sudden, random aggression towards inanimate objects or empty spaces. The dog growls and barks while facing a wall.

Former medical records were not available for review.

Physical examination was unremarkable.

A complete neurological examination was performed and revealed depressed mental status, central blindness (bilaterally absent menace responses, intact pupillary light reflexes and absent visual tracking) and bilaterally absent nasal mucosal nociception. The remainder of the neurological examination was within normal limits.

Neuroanatomical localisation was consistent with bilateral forebrain disease. Left lateralisation was considered possible based on the history of circling to the left.

Inflammatory (e.g., meningoencephalitis of unknown aetiology [MUA]), infectious (e.g., bacterial, fungal, rickettsial or viral meningoencephalitis), metabolic (e.g., hepatic encephalopathy, hypoglycaemic encephalopathy), degenerative (e.g., lysosomal storage diseases, mitochondrial encephalopathies, organic acidurias) or neoplastic (e.g., primary or secondary brain tumours) diseases were considered.

INVESTIGATIONS

Routine haematology, serum biochemistry, electrolytes, urine analysis and culture were performed and did not reveal significant abnormalities. There was a mild increase in DGGR lipase (134 IU/L; reference range: 6–63) in the absence of clinical signs suggestive of pancreatic disease.

Magnetic resonance imaging (MRI; SIGNA Voyager 1.5 Tesla, GE Healthcare MRI Scanner) of the brain was structurally unremarkable, and cerebrospinal fluid (CSF) analysis collected via cerebellomedullary cistern puncture was normal with a nucleated cell count of less than 1/μL (reference range: 0–5) and protein content of 0.16 g/L (reference range: <0.3). Genetic testing for mutation in the canine PPT1 gene was also performed and was homozygous for the wild-type allele.

LEARNING POINTS/TAKE-HOME MESSAGES

- Neuronal ceroid lipofuscinosis should be considered as a differential diagnosis, regardless of breed and age, in cases of progressive visual impairment, abnormal and/or aggressive behaviour, cognitive or motor decline, cerebellar ataxia, sleep disturbances and seizures.
- More breeds and different phenotypes of neuronal ceroid lipofuscinosis seem yet to be described in veterinary patients—the disease is not confined to patients with a young age of onset of clinical signs.
- Postmortem examinations and sampling of neuronal and non-neuronal tissues should be encouraged in all patients suspected of neuronal ceroid lipofuscinosis. Whole-genome sequencing will play a role in future investigations of these cases.

TREATMENT

Given the inconclusive results of investigations, degenerative diseases, including lysosomal storage diseases, were considered the main differential diagnosis. However, as up to 7% of dogs affected with MUA can have an unremarkable MRI scan and between 3% and 57% might have normal CSF analysis,[17] MUA was still considered a possible differential diagnosis. For this reason, a trial with immunosuppressive doses of corticosteroids was initiated (prednisolone 2 mg/kg per os every 24 hours), to assess for any response to suggest occult inflammatory central nervous system (CNS) disease.

OUTCOME AND FOLLOW-UP

Despite treatment, the dog's neurological condition continued to deteriorate over the following week. The frequency of the aggressive episodes continued to increase, and new autonomic signs (hypersalivation) started to be noticed following some of these episodes, possibly suggesting the presence of seizure activity. Antiepileptic medication (levetiracetam 250 mg per os every 8 hours) was therefore trialled—no improvement was seen.

Due to the ongoing deterioration, euthanasia was elected 10 days after initial presentation.

On postmortem examination, the cerebrum was macroscopically normal. Microscopically, small to moderate numbers of neurons located in the cerebrum and the pons were mildly swollen and contained intracellular pale brown granular material with haematoxylin and eosin stain (Figure 1a). The granular material was autofluorescent (Figure 2), periodic acid–Schiff (PAS)-positive, weakly Luxol fast-blue-positive and acid-fast negative (Figure 1b–d). Affected neurons were subjectively more frequent in the thalamus and hypothalamus. To confirm the ultrastructure and location of the granular material, scanning electronic microscopy was conducted on a formalin-fixed tissue sample from the thalamus. Multiple variably sized electron-dense granules were identified along with lipid droplets and acicular electron-lucent components

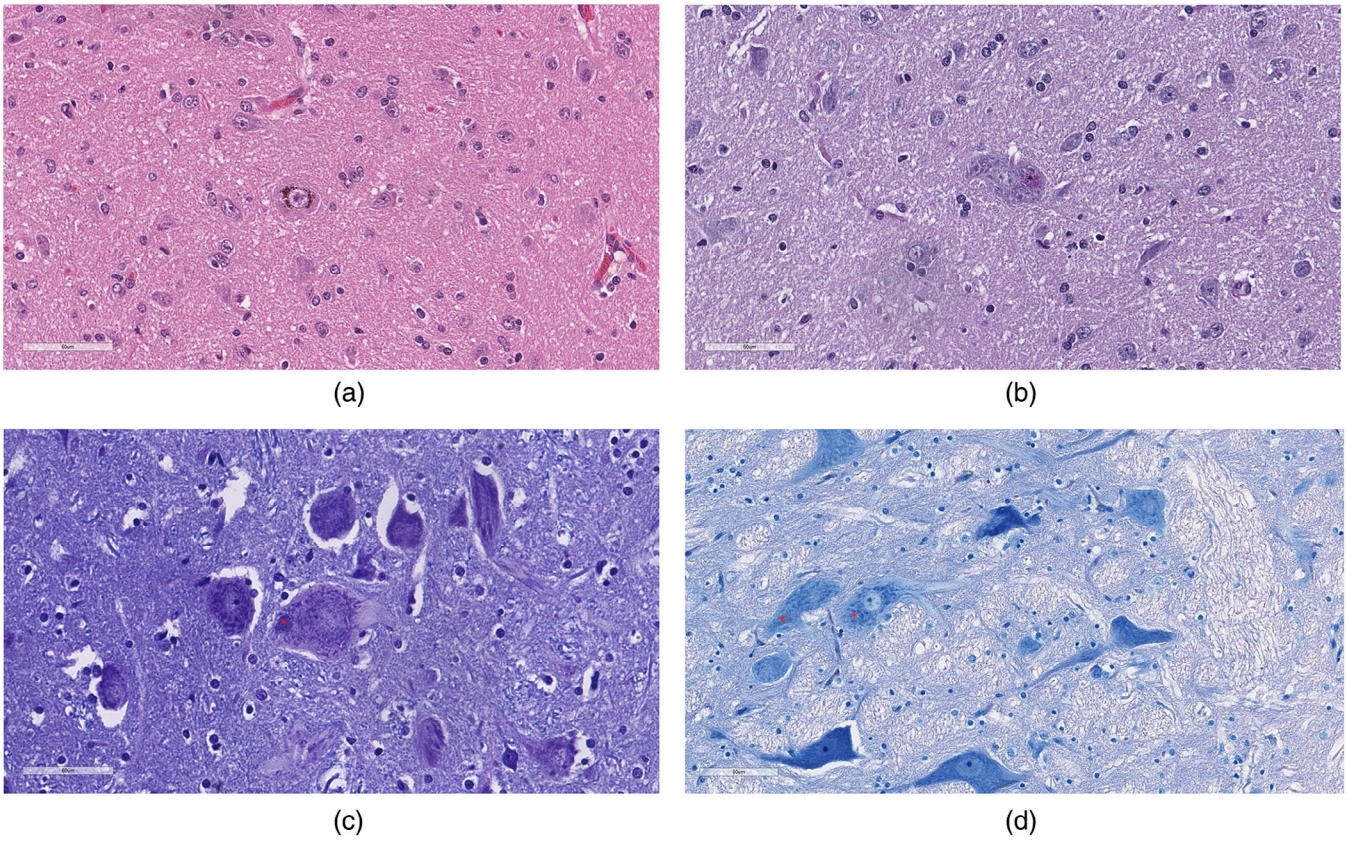

FIGURE 1 Histomicrograph of brain at the level of thalamus. (a) Some neurons show cytoplasmic light brown granules. Haematoxylin and eosin stain. (b–d) Cytoplasmic granules (asterisk) are: periodic acid–Schiff stain-positive (b), weakly Luxol fast-blue-positive (c), and acid-fast (Ziehl-Neelsen stain)-negative (d).

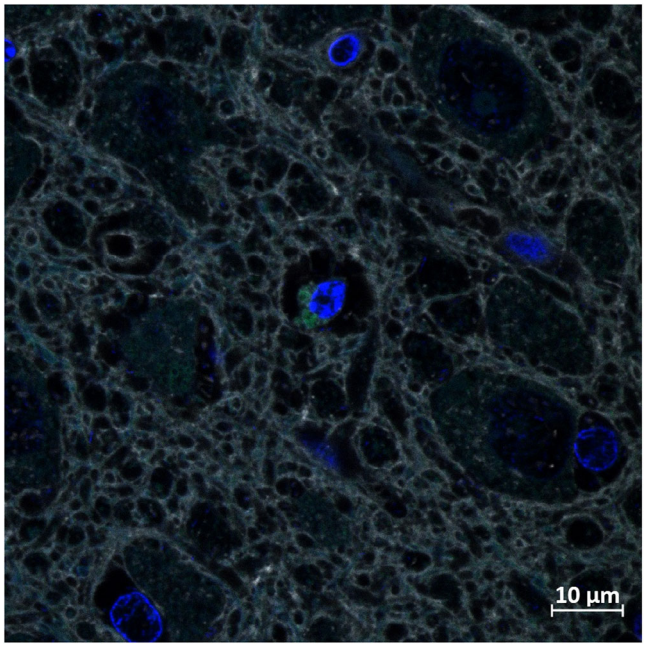

FIGURE 2 Confocal image of deparaffinised tissue section at the level of the hypothalamus stained with Hoechst nuclear stain and Wheat Germ Agglutinin (WGA) Alexa fluor 647 conjugate. WGA-Alexa fluor 647 is shown in grey, Hoechst 33342 in blue, autofluorescence in green and transmitted light in greyscale.

(Figure 3a,b). The microscopic findings were compatible with the diagnosis of NCL.

Further genetic testing was performed on formalin-fixed paraffin-embedded scrolls from the cerebrum, revealing homozygous wild-type alleles in the PTT1 and TPP1 canine genes.

DISCUSSION

Historically, subclassification of NCLs in human medicine was performed according to the age of onset, clinical features and demonstration of lysosomal storage material by electronic microscopy.[18]

A classification based on age of onset of clinical signs is less straightforward to perform in veterinary medicine due to the variability between different breeds of dogs, with smaller dogs reaching skeletal, behavioural and social maturity earlier than large breed dogs.[19,20] In addition to this, the clear time of onset of clinical signs associated with NCL might also be difficult to define in some patients, as initial signs may be non-specific or overlap with many other diseases and have an insidious onset (e.g., subtle behavioural changes or visual impairment). In the present case, an adult onset of disease was considered, as the clinical signs were initially reported in a fully grown and sexually mature dog.

The diagnosis of NCL should be initially suspected in cases where there is evidence of heritability, presence of progressive neurological signs (often encompassing vision loss, abnormal and/or aggressive behaviour, loss of learned behaviours, tremors, cerebellar ataxia, decline in cognitive and motor functions, changes in sleeping patterns and seizures), and after the detection of accumulations of storage material in the neuronal tissues.[1]

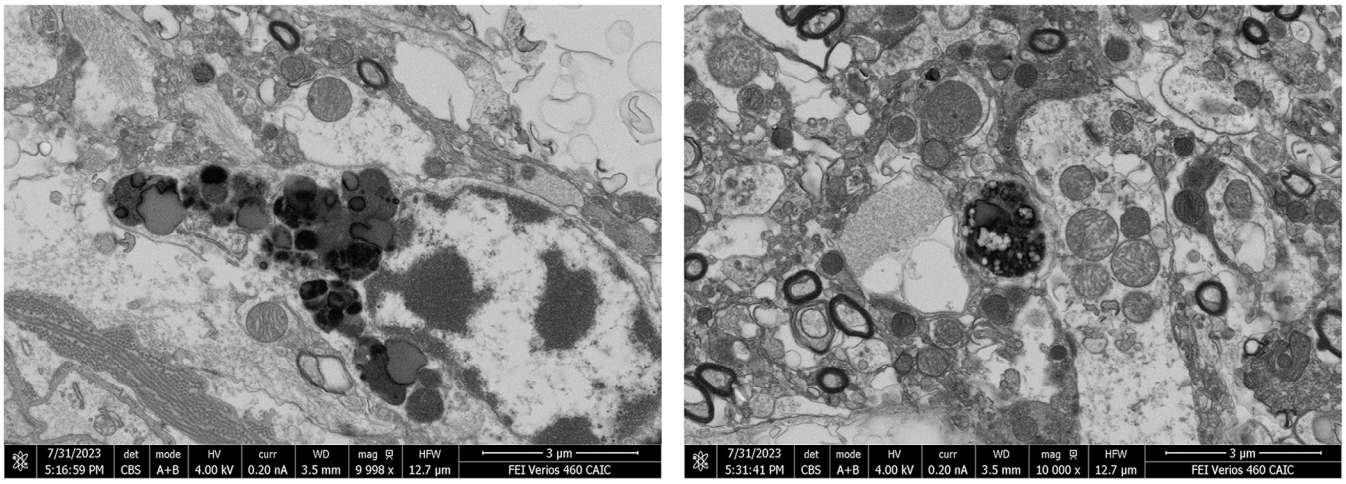

FIGURE 3 Scanning electron microscopy of lipofuscin granules in the brain. Dense deposits are apparent in the cytoplasm adjacent to the nucleus (a). Associated with some deposits are electro-lucent vacuoles (b).

With the advancement of genetic testing and discovery, many NCLs can now be classified based on the causative mutant gene that leads to the disease.[7] This classification can allow the identification of possible carriers of the defected gene, helping to screen dogs for this disease before the onset of clinical signs or before entering a breeding programme. However, the identification of novel causative mutation first requires histopathology to diagnose NCL. The emotional impact on owners linked to postmortem examinations, coupled with the high cost of whole-genome sequencing (WGS) pose constraints on advancements in this field.

There are three previous reported cases of adult onset of NCLs in the dachshund breed. Cummings and de Lahunta[15] described a 3-year-old, female, spayed, wire-haired dachshund with slowly progressive gait abnormalities consisting of truncal ataxia and hypermetria, suggestive of cerebellar disease. Microscopic examination of haematoxylin–eosin preparations revealed a widespread loss of Purkinje cells and accumulation of intracellular gold granules in variable amounts throughout the neuroaxis, which were autofluorescent and PAS-positive. Electronic microscopy (EM) of the affected neurons predominantly revealed pleomorphic lipid bodies often arranged in parallel and forming one or more series of lamella. Zebra, compound, membranous cytoplasmatic bodies and typical lipofuscin bodies were identified less frequently.

Vandevelde and Fatzer[16] reported two other cases of adult onset of NCL in a 5-year-old and a 7-year-old long-haired dachshund. Occasional generalised seizures progressing to behavioural changes, dullness, polyphagia and polydipsia were reported in one of these dogs, while the other presented with compulsive walking and generalised seizures. In these dogs, accumulation of ceroid lipofuscin led to atrophy of the cerebellar granular cell layer, but the Purkinje cells were relatively spared. EM identified cytosomes containing mainly membranous material arranged in crescent shapes or parallel stacks and fingerprint patterns. Zebra bodies were rare. Less commonly, granular and amorphous material was also found. MRI of the brain was not performed in any of these cases, and as genetic testing was not available, further characterisation of the disease in these patients was not possible.

There are significant differences in the clinical signs, distribution of granules in the nervous system and EM findings between these previously reported cases. These also have distinct clinical features from the present case, which showed clinical signs suggestive of forebrain disease, and the accumulation of intracellular deposits were more frequent in the thalamus, hypothalamus and pons. Ultrastructurally, the deposits in the current case were amorphous granular, and occasionally incorporated lipid-like vacuoles and clefts as described in some cases of lipofusin accumulation.[21,22] Lipofuscin pigments are a heterogenous group of compounds, which might explain the variable morphological features previously described.[23] In the present case, as EM was performed on formalin-fixed tissues, a degree of distortion was also considered possible. These dissimilarities suggest a possible different subclassification of NCL between our patient and the previously reported cases of dachshunds with adult-onset NCL.

Mutations in two canine genes (TPP1 and PPT1) have been identified as causative for the development of NCL in dachshund dogs.[5,6] Sanders et al.[5] described the occurrence of NCL associated with a mutation in the TPP1 canine gene in two juvenile dachshund siblings. Progressive neurological signs were noted at 7–9 months of age, and included mental dullness, loss of learned commands, ataxia, visual impairment, aggressive behaviour, hypermetric gait, compulsive circling and seizures. Both dogs died at 1 year of age due to progression of their disease. Postmortem examination of one of these dogs revealed autofluorescent storage bodies throughout the CNS (cerebral cortex, cerebellum and spinal cord), and electronic microscopy revealed mainly curvilinear forms of storage body materials.

More recently, Awano et al.[6] described a case of NCL in a 9-month-old dachshund with signs of abnormal behaviour (nervousness, loss of learned commands, decreased interaction with environment, inappropriate vocalisation), sensitivity to loud noise, tremors, ataxia, visual impairment and generalised weakness. This dog was euthanased at 14 months of age, and genetic analysis identified a genetic mutation on the PPT1 canine gene. The accumulation of the storage material in the cerebellum was more evident in the granular layer rather than the Purkinje cells, as reported in other cases of NCL.[5,8–10,15]

Although the clinical signs of the reported dachshunds with the TPP1 and PPT1 mutations are similar to those observed in our case, an earlier onset of clinical signs (<1 year old) makes the current case unique. A mutation in the PPT1 gene has also been identified in a 10-month-old Cane Corso with NCL,[11] showing these genetic mutations can also affect diverse breeds. It therefore follows that the current included case could be affected by one of the other known mutations responsible for NCL in other breeds; however, these were not analysed because of financial limitations. Considering the possibility of identifying a novel causative genetic mutation for NCL, WGS was also contemplated in this case; however, due to the unavailability of suitable stored samples it was not possible.

NCLs associated with mutations in the ATP13A2 canine gene are characterised by the onset of clinical signs later in the mature dog's life.[13] This was previously described in Australian cattle dogs that seem to become affected at approximately 6 years of age.[13] Tibetan terrier dogs can also be affected with this mutation; the disease phenotype appears to be uniform and characterised by onset of clinical signs at 5–7 years of age and including abnormal behaviour (e.g., aggression, anxiety), ataxia, tremors, seizures and vision loss.[13,14] These phenotypical similarities make this gene a potential candidate causative mutation in the current case. The reason for the late onset of the disease is not clear, but it is suspected to be multifactorial, with multiple genetic factors interacting with multiple environmental factors, during extended periods of time, leading to the production of a specific phenotype.[24] Genetic factors might include variable penetrance and expressivity (when not all individuals with a specific genetic mutation display the same clinical phenotype), locus or allele heterogenicity (when mutations in different genes or different mutations in the same gene lead to a similar disease phenotype, with possible differences in severity or age of onset of clinical signs).[25]

Development of aggressive behaviour appears to be a frequent feature in canine NCL.[7,8,10,13,26] Aggressive behaviour is also reported in human patients with juvenile NCL.[27,28] Canine aggression is usually related with behavioural conditions that can be influenced by intrinsic (e.g., breed, sex, neuter status) and extrinsic/environmental factors (e.g., owner's characteristics, living situation, owner interaction and methods of reprimand).[29] However, structural brain disease with neoplastic, infectious (canine distemper, rabies) or congenital (lissencephaly, hydrocephaly) causes can lead to an increase in aggressiveness. This seems particularly true when lesions are in the frontal cortex, hypothalamus, thalamus, amygdaloid body, medial mamillary nucleus, habenular nuclei, hippocampus or the caudate nucleus.[30] The prevalence of accumulated material in the thalamus and hypothalamus in the case reported here may explain the aggressive behaviour witnessed.

Although previous medical records were not available, it was presumed that the patient had been vaccinated against rabies, as this is a requirement for entry into the United Kingdom. Furthermore, as the United Kingdom is considered a rabies-free country, infection by the virus was deemed extremely unlikely in this case.

The progression of the clinical signs and consequent euthanasia of the present case were much more rapid compared to some other reports of NCL in dogs.[13,31,32] However, timing for euthanasia in dogs can also vary significantly due to the natural variability in tolerance of the owners to cope with their pet's clinical signs. As the case here was showing significant aggressive behaviour and was also currently being housed by a foster-charity, the tolerance for abnormal behaviour was likely to be lower than in an owned pet with more manageable clinical signs.

The involvement of tissues beyond the CNS is a recognised feature of lysosomal storage diseases.[33] This involvement can impact both the clinical manifestation of the disease and the accessibility of tissues for diagnostic purposes. Although there appears to be high variability in the distribution of intracellular deposits among different dogs, breeds or subclassifications of the disease,[7] the number of reported cases assessing this distribution remains limited. Cellular functional impairment outside the CNS is often overlooked due to the predominance and severity of neurological signs. Nonetheless, if patients survive long enough, progressive development of non-neurological disease is expected. Therapeutic interventions focused solely on the CNS (e.g., intracerebroventricular gene therapy) may therefore be insufficient to adequately treat these diseases, and systemic therapy might also be necessary.[34]

A more comprehensive understanding of the distribution of accumulated storage products across a wider range of cases could help in better categorising these diseases, potentially facilitating their diagnosis through the analysis of more readily available extra-neuronal tissues. This understanding could also guide future genetic testing and treatment trials, providing models for treatment in humans. Therefore, histopathological analysis of extra-neural tissues such as eyes, spleen, liver and heart should be considered in all patients suspected of having NCL. Body tissues outside the CNS (including the eyes) were not available for histopathological analysis in this patient, and for this reason it was not possible to further classify the disease distribution in non-neural tissues.

This report characterises the clinical signs, diagnostic investigation and imaging findings, as well as postmortem histopathological and ultrastructural changes, in a smooth-haired dachshund with an adult onset of clinical signs attributable to NCL. The dog was negative for both previously reported mutations associated with NCL in the breed and had distinct clinical and ultrastructural features. The authors propose this case to represent a novel appearance of NCL in the dachshund breed, caused by a distinct but not yet identified genetic mutation.

AUTHOR CONTRIBUTIONS

Diogo Gouveia: conceptualisation; writing—original draft; writing—review and editing. **Max Foreman**: conceptualisation; supervision; writing—review and editing. **Emilie Cloup**: conceptualisation; analysis and interpretation of histopathological data; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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ETHICS STATEMENT

Authors declare human ethics approval was not needed for this study.

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