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Neurological signs and imaging findings in two American Staffordshire Terrier dogs diagnosed with neuronal ceroid lipofuscinosis 4A: First report of the presenceof the *ARSG* gene mutation in Brazil

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ABSTRACT: Neuronal ceroid lipofuscinosis 4A (NCL4A) is a rare hereditary neurodegenerative disease that affects adult American Staffordshire Terriers (AST) leading to progressive late onset signs of typical cerebellar deficits. We report for the first time in Brazil, the presence of the causative mutation for NCL4A in the *ARSG* gene in two AST, the neurological signs and imaging findings. Both dogs were presented with a late onset progressive cerebellar deficits. Magnetic resonance imaging scan (MRI) and cerebrospinal fluid analysis were performed in both cases at the initial clinical course and no abnormalities were found. One dog was submitted to a new MRI three years later and cerebellar atrophy was evident. Both dogs were tested for the causative mutation for NCL4A in the *ARSG* gene and were both positive. NCL4A should be considered the main differential diagnosis in an adult AST presenting a late onset progressive cerebellar deficits. Cerebellar atrophy on MRI scan reinforces the suspicion, but confirmation of the causative genetic mutation in the *ARSG* gene remains the gold standard antemortem diagnosis for NCL4A in the AST.
Key words: hereditary ataxia, lysosomal storage disease, NCL4A, cerebellar atrophy, American Staffordshire Terrier.

Sinais neurológicos e achados de imagem em dois cães American Staffordshire Terrier diagnosticados com lipofuscinose ceroide neuronal 4A: Primeiro relato da presença da mutação no gene *ARSG* no Brasil

RESUMO: Lipofuscinose ceroide neuronal 4A (NCL4A) é uma doença neurodegenerativa hereditária rara que afeta American Staffordshire Terriers (AST) adultos, levando a sinais progressivos de déficits cerebelares com um início tardio. Descreve-se pela primeira vez no Brasil, a presença da mutação causadora de NCL4A no gene *ARSG* em dois AST, os sinais neurológicos e achados de imagem. Ambos os cães apresentaram déficits cerebelares progressivos de início tardio. A ressonância magnética (RM) e a análise do líquido cefalorraquidiano foram realizadas em ambos os casos no início dos sinais clínicos e nenhuma anormalidade foi encontrada. Um cão foi submetido a uma nova RM três anos depois e atrofia cerebelar ficou evidente. Ambos os cães foram testados para a mutação no gene *ARSG* causadora da NCL4A e ambos foram positivos. NCL4A deve ser considerada o principal diagnóstico diferencial em um AST adulto que apresente déficits cerebelares progressivos de início tardio. A atrofia cerebelar na RM reforça a suspeita, mas a confirmação da mutação genética no gene *ARSG* continua sendo o diagnóstico *antemortem* padrão ouro para NCL4A no AST.
Palavras-chave: ataxia hereditária, doença do acúmulo lisossomal, NCL4A, atrofia cerebelar, American Staffordshire Terrier.

INTRODUCTION

Neuronal ceroid lipofuscinosis 4A (NCL4A) is a rare neurodegenerative disease with a slow progression that belongs to the group of lysosomal storage diseases and, within the hereditary ataxias, was recently included in the category of multifocal degenerative diseases with predominant spino-cerebellar signs (STEE et al., 2023). It affects American Staffordshire Terriers (AST) and Pit Bull Terriers and, despite being hereditary, the neurological signs have a late onset, becoming evident between 3 and 6 years (range: 18 months to 9 years) of age in both breeds (OLBY et al., 2004; ABITBOL et al., 2010). Affected individuals will present typical cerebellar signs such as ataxia, truncal sway, wide base stance, hypermetria, spontaneous nystagmus, abnormal menace response, difficulties negotiating stairs and episodes of falling with transient opisthotonus (OLBY et al., 2004). In advanced cases, magnetic resonance imaging scan (MRI) of the brain may reveal diffuse cerebellar atrophy and cerebrospinal fluid (CSF) analysis either are within reference range or present a mild albuminocytological dissociation (OLBY

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et al., 2004; KWIATKOWSKA et al., 2013). Other ancillary tests such as brainstem auditory evoked responses can reinforce the suspected diagnosis of NCL4A (KWIATKOWSKA et al., 2013).

The suspected diagnosis is reinforced by the identification of the genetic mutation in the *ARSG* gene (ABITBOL et al., 2010) and the definitive diagnosis given by histopathology (postmortem) (SISÓ et al., 2004; NOLTE et al., 2016). Prognosis is poor, as with continued progression of the disease, dogs became unable to walk without falling repeatedly and are ultimately submitted to euthanasia within 2 to 4 years after clinical onset (range: 6 months to 6.5 years) (OLBY et al., 2004). The aim of this report is to describe for the first time in Brazil, the presence of the causative mutation for NCL4A in the *ARSG* gene in two AST, the neurological signs and imaging findings.

Case 1

A 7-year-old male castrated AST was presented to a private veterinary practice located in the city of Florianópolis, south Brazil, for neurological examination due to progressive signs of lack of balance that has started 3 years previously. General clinical examination was unremarkable. On neurological examination, performed by a European board-certified veterinary neurologist, the dog showed evident generalized vestibulocerebelar ataxia, truncal and head sway, wide base stance, hypermetria, difficulties in negotiating stairs, spontaneous horizontal nystagmus and positional rotatory nystagmus and decreased menace response bilaterally. The dog also showed episodes of transitory opisthotonus after shacking its head (Figure 1). The neurolocalization was diffuse cerebellum.

Complete blood count (CBC), serum biochemistry panel and urinalysis were within the reference range. At the beginning of the clinical symptoms, the dog was submitted to an MRI of the brain, which did not reveal any abnormalities (Figure 2A). CSF analysis was also performed and showed no alterations, as well as the PCR test, which was non-reactive for the main infectious diseases. However, due to progression of the neurological signs, a new MRI was performed 3 years after the first one, which then revealed evident cerebellar atrophy with a compensatory increase in the volume of the 4th ventricle and cisterna magna (Figure 2B) and slight brain atrophy with slight asymmetrical dilation of the lateral ventricles (Figure 3). Another CSF analysis was performed and showed no alterations. Based on the history, anamnesis, neurological examination, progression of the clinical signs and imaging findings in the second MRI, NCL4A was the main suspicion. Due to the absence of specific genetic testing for the *ARSG* gene mutation in Brazil at the time when the second MRI was performed, the dog was tested for one of the only genetic mutations available in the country for lipofuscinoses in dogs, the mutation in the *CLN5* gene, responsible for the development of ceroid lipofuscinosis 5 in Golden Retrievers. This test was negative in this dog. A blood sample was then sent to a European laboratory (LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany) for specific testing for the *ARSG* gene mutation, which confirmed that the tested animal was homozygous for the causative mutation for NCL4A in the *ARSG* gene. Until the publication of this case report, this dog was still alive, ambulatory and with a satisfactory quality of life despite the severity of the neurological signs.

Case 2

A 6-year-old female neutered AST was presented to a private veterinary practice located in the city of Florianópolis, south Brazil, for neurological

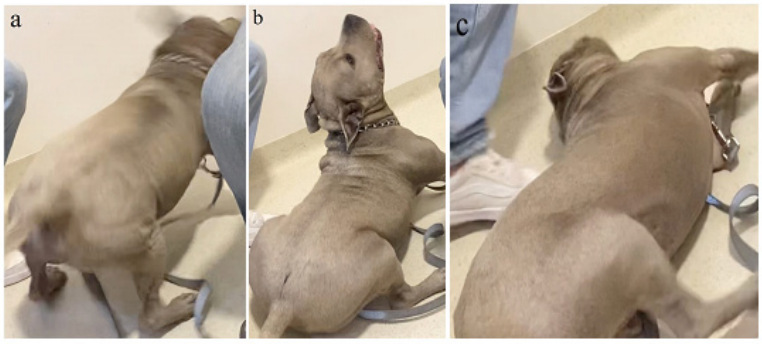

Figure 1 - American Staffordshire Terrier dog (case 1) with neuronal ceroid lipofuscinosis 4A. Note after head shaking (a), transient opisthotonus (b), followed by falling (c).

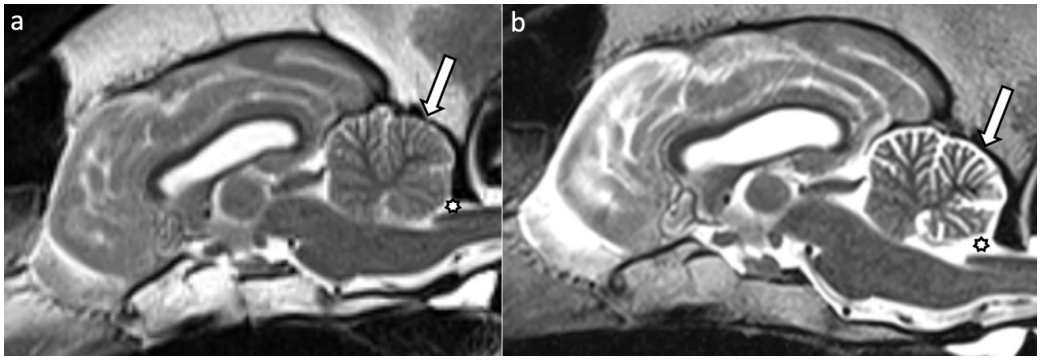

Figure 2 - Magnetic resonance imaging: sagittal T2-weighted sections of an American Staffordshire Terrier diagnosed with neuronal ceroid lipofuscinosis 4A at the onset of clinical signs (a) and 3 years later (b). In (a), the cerebellum (arrow) and cisterna magna (white star) do not show any evident abnormalities. In (b), there is evident cerebellar atrophy, characterized by decreased cerebellar volume and widening of the cerebellar fissures (arrow). There is also a compensatory increase in the volume of the cisterna magna and 4th ventricle (white star).

examination due to progressive neurological signs. The main complaint was a progressive lack of balance going on for 2 years. General clinical examination was unremarkable. On neurological examination, performed by a European board-certified veterinary neurologist, the dog showed moderate generalized vestibulocerebelar ataxia, truncal and head sway, intermittent wide base stance, difficulties in negotiating stairs, positional vertical nystagmus, decreased menace response bilaterally and episodes of transitory opisthotonus after shacking its head. Neurolocalization was diffuse cerebellum. CBC, serum biochemistry panel and urinalysis were within the reference range. When the clinical symptoms first appeared, the dog underwent an MRI of the brain and CSF analysis, both of which showed no abnormalities. Based on the history, anamnesis, neurological examination and progression of the clinical signs, NCL4A was the main suspicion. A blood sample was sent to the same European laboratory (LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany) as in case 1 for specific testing for the *ARSG* gene mutation, which also confirmed that case 2 was homozygous for the causative mutation for NCL4A in the *ARSG* gene. Until the publication of this case report, this dog was also still alive, ambulatory and with a satisfactory quality of life despite the evident cerebellar signs.

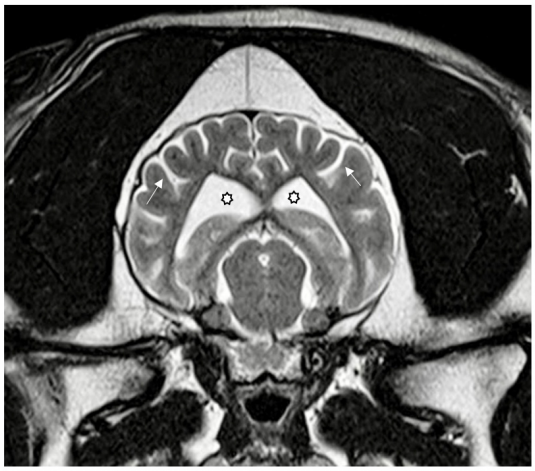

Figure 3 - Magnetic resonance imaging: transverse T2-weighted section at the level of the midbrain of an American Staffordshire Terrier diagnosed with neuronal ceroid lipofuscinosis 4A. Note the slight brain atrophy characterized by the prominent cerebral sulci (white thin arrows) and the slight asymmetrical dilation of the lateral ventricles, with the left ventricle being larger than the right ventricle (white stars).

The phenotype and the causative genetic basis of several neuronal ceroid lipofuscinosis (NCL) are well described in human medicine (GARDNER & MOLE, 2021). In veterinary medicine, many species have been reported with NCL and, in the past two decades, this condition has been increasingly recognized in several dog breeds, including their causative genetic variants (KATZ et al., 2017). Besides the AST, NCL with a known causative mutation has been reported in Border Collies (*CLN5* gene) (MELVILLE et al., 2005), Dachshund (*TPP1* gene) (AWANO et al., 2006a), American Bulldogs (*CTSD* gene) (AWANO et al., 2006b), Australian shepherd (*CLN6* gene) (KATZ et al., 2011), Tibetan terriers (*ATP13A2* gene) (FARIAS et al., 2011), Chinese crested dog (*MFSD8* gene) (GUO et al., 2015), Golden Retrievers (*CLN5* gene) (GILLIAM et al., 2015), Chihuahua (*CLN7* gene), (FALLER et al., 2016), Australian Cattle dogs (*CLN5* gene) (KOLICHESKI et al., 2016) and most recently

in the Schapendoes dog (*CLN6* gene) (BELLAMY et al., 2024). Interestingly, Pit Bull Terriers also develop NCL4A due to the same genetic variant in the *ARSG* gene seen in the AST, showing similar late onset clinical signs and similar progression (ABITBOL et al., 2010; STEE et al., 2023). Many other breeds with NCL are reported in the literature and this number will probably increase over the years. The advances in DNA sequencing and data analysis have made the full canine genome and its annotations available, making whole-genome sequencing a very efficient method, allowing screening of all known NCL genes and the discovery of new mutations in other genes (KATZ et al., 2017). Regardless of the breed affected, the phenotype of NCL in dogs is very similar and is mainly characterized by progressive neurological signs, including blindness, abnormal behavior, sleep disturbance, epileptic seizures and cerebellar signs (ataxia, tremors) (KATZ et al., 2017), the latest, a key feature in AST with NCL4A.

NCL4A in the AST was previously termed "cerebellar cortical degeneration" and has been reported sporadically in Europe and in the United States (HANZLÍČEK et al., 2003; OLBY et al., 2004; BUIJTELS et al., 2006; ABITBOL et al., 2010; KWIATKOWSKA et al., 2013). In Brazil, there is a single report of a 10-year-old female AST that was presented with a 3-year history of progressive cerebellar signs and on postmortem examination, cerebellar abiotrophy was diagnosed (MARI et al., 2014). A similar report from Uruguay described a 6-year-old female AST, with signs of ataxia and tremors. Due to the progression of the neurological signs, the dog was euthanized and on postmortem examination, the histopathological findings were compatible with cerebellar abiotrophy (VERDES et al., 2020). Neither of these two dogs underwent genetic testing, and despite the marked histopathological findings consistent with cerebellar abiotrophy, it remains unclear whether they were homozygous for the causative NCL4A mutation in the *ARSG* gene.

According to the authors, this is the first report of the presence of the causative mutation for NCL4A in the *ARSG* gene in AST in Brazil, where we describe the neurological signs and imaging findings in two cases.

Both cases presented here were adult AST showing late onset cerebellar signs with a very slow progression. This presentation is typical in dogs affected by NCL4A (OLBY et al., 2004), but other differential diagnoses for progressive cerebellar signs in an adult dog should be considered, including neoplastic processes, especially tumors affecting the cerebellopontine angle (KALDRYMIDOU et al., 2001; STURGES et al., 2008) and inflammatory infectious cerebellar diseases, such as distemper (GRIFFIN IV et al., 2009), toxoplasmosis (AVERILL & DELAHUNTA, 1971) and neospora (KENNEDY et al., 2024). Both dogs in this report were submitted to an MRI scan of the brain and CSF tap at the initial clinical onset, including PCR from CSF in case 1, which was negative for distemper, toxoplasmosis and neospora. Based on these findings, an inflammatory infectious disease affecting the cerebellum or a neoplastic process were considered less likely to be the cause of the ongoing clinical signs.

Despite the severity of the neurological signs, both dogs were still ambulatory and with a satisfactory quality of life. Unfortunately, most affected AST, due to the progression of the disease, will become nonambulatory within 2 to 4 years after onset of neurological signs (range: 6 months to 6.5 years) (OLBY et al., 2004; STEE et al., 2023). Both cases 1 and 2 underwent brain MRI at the onset of clinical signs, and in both dogs no abnormalities were observed. In case 1, a second MRI was performed 3 years after the first one, and generalized atrophy of the cerebellum was then evident, accompanied by a compensatory increase in the volume of the 4th ventricle and cisterna magna, also described in other affected dogs (OLBY et al., 2004; HENKE et al., 2008; KWIATKOWSKA et al., 2013). Although diffuse cerebellar atrophy is a common finding in these cases (OLBY et al., 2004; STEE et al., 2023), mild or no abnormalities may be seen in the MRI at the initial clinical onset, but might become evident over time as the clinical signs progresses. This characteristic has been recently described in a cat with progressive cerebellar cortical degeneration, where a follow-up MRI showed evident cerebellar atrophy, which was not apparent in a first MRI and was attributed to the slow progression of the clinical signs (GIRON et al., 2024). Affected AST with more severe clinical signs tend to have a smaller relative cerebellar size (brain:cerebellum ratio) in comparison to dogs with mild clinical signs and although these differences were not statistically significant (HENKE et al., 2008), this reinforces our suspicion that an MRI performed at the initial clinical onset, may be normal in cases of NCL4A.

The suspected diagnosis of NCL4A in both dogs was based on the presence of a mutation in the *ARSG* gene, responsible for the development of this disease in the AST (ABITBOL et al., 2010). The mutation in the *ARSG* gene is reported to cause a 75% decrease of function of arylsulfatase G (ABITBOL et al., 2010), which has an important role in the catabolism of mucopolysaccharide heparan sulfate (KOWALEWSKI et al., 2012). In rare cases, some

dogs may present a subclinical form of the disease (1-3%) and around 50% of the AST population are considered healthy carriers of this mutation (ABITBOL et al., 2010). Both case 1 and case 2 were homozygous for the causative mutation for NCL4A in the *ARSG* gene, confirming the diagnosis. Affected individuals are probably bred before the appearance of the clinical signs due to its late onset characteristics, which probably led to a wide dissemination of the disease within the AST population, as most affected dogs in the United States and Europe, have a closest common ancestor born in the 1950s (OLBY et al., 2004). Pedigrees were obtained from both dogs. They were acquired from the same breeder and although they were from different lineage, these dogs had a closest common ancestor born in 1998 with its origin in the United States.

In conclusion, NCL4A should be among the main differential diagnoses in young-adult AST presenting with a slow progressive course of cerebellar deficits. MRI of the brain provides valuable information regarding cerebellar atrophy in severely affected dogs, but should not be used to exclude the disease as no abnormalities may be seen in the initial course; therefore, relying solely on a single MRI at a single time point may prove insufficient, and for this reason, a follow-up examination can be useful as the disease progresses. Identification of the *ARSG* gene mutation via specific genetic test is the gold standard antemortem diagnosis for NCL4A and this case report has demonstrated for the first time that this variant is present in the AST lineage in Brazil. The recognition of this disease in AST and the availability of these genetic tests in Brazil are essential for a definitive antemortem diagnosis and, in addition, it helps control the progression of the disease in this specific population of dogs.

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DECLARATION OF CONFLICT OF INTEREST

There are no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

All authors contributed equally to the conception and writing of the manuscript. All authors critically reviewed the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was used in a careful manner for the revision and improvement of the manuscript's quality, without any alteration to the scientific content.

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