L-2-hydroxyglutaric aciduria: canine progressive neurological dysfunction

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Anita Theobald discusses the clinical signs associated with this disorder, and looks at the diagnostic hallmarks of a condition associated with a gene mutation

L-2-HYDROXYGLUTARIC aciduria (L-2-Hga) is a metabolic disorder resulting in progressive neurological deterioration. While it was first described in humans in 1980[1], the first report in a non-human species was not until 2003.

Six Staffordshire bull terriers showed neurological symptoms associated with marked elevations of L-2-hydroxyglutaric acid in urine and cerebrospinal fluid (CSF)[2]. Since that time, it has been reported in further Staffordshire bull terriers[3,4], a West Highland white terrier[5] and a Yorkshire terrier[6].

L-2-HGA is inherited as an autosomal recessive disease in both dogs and humans, with related dogs being reported to be affected[2,4]. Genetic investigations in Staffordshire bull terriers have revealed the condition to be associated with two single substitution mutations within exon 10 of the gene encoding for L-2-hydroxyglutarate dehydrogenase (L2HGDH)[4]. This enzyme is responsible for converting L-2-hydroxyglutarate to 2-oxoglutarate during the Krebs cycle. Similar studies in humans have found mutations within the same gene[7,8]. Although the specific pathway for the metabolism of L-2-hydroxyglutaric acid and the cause of its neurotoxic effects is unknown, it is suspected that the pathological effects witnessed in L-2-HGA are caused by oxidative stress from L-2-hydroxyglutaric acid build-up within the tissues of the brain[9], and interference with creatine kinase activity within the cerebellum[10].

Affected humans typically present during childhood, although several reports of adultpresentation have been documented[11],[12],[13]. Humans display progressive learning disabilities, psychomotor disorders, seizures and growth retardation. Sudden death has been reported in neonates[14] and infants[15].

Clinical signs in dogs

While L-2-HGA is generally considered to be a progressive disease of insidious onset, affecting young humans and dogs, there are reports of an acute onset of clinical signs (in the form of generalised tonic-clonic seizures)[2] and an adult presentation[2],[5].

In one seven-year-old dog, gait abnormalities had not been noted by the dog's owners and were only identified on veterinary examination[2]. Anecdotally, a five-year-old Staffordshire bull terrier was recently diagnosed with this condition after its owners had dismissed its abnormal gait since a puppy as "clumsiness".

Cerebral dysfunction is a consistent clinical finding in affected dogs, with development of abnormal behaviours (including loss of obedience, difficulty training, wall-staring, head-pressing, excessive attention – seeking, aggression and lethargy), generalised tonicclonic seizures, vision impairment and postural reaction deficits.

Signs of cerebellar dysfunction are also documented, with ataxia, hypermetria, head and neck tremors and decreased menace responses reported. Brainstemlesions may be a further cause of ataxia. One Staffordshire bull terrier also presented with muscle stiffness and exerciseinduced fatigue[2].

Abnormal postures may also be present when the dog is standing still (Figure 1).

Diagnostic findings

Routine clinical pathology (haematology and biochemistry profiles, urinalysis and faecal analysis) findings are normal in affected dogs.

Magnetic resonance imaging (with all reported investigations performed at 1.5 Tesla) have thus far invariably revealed bilaterally symmetrical and diffuse increased T2-weighted signal intensity within the cerebral and cerebellar cortices, thalamus and brainstem[2]-[6]. In addition, particular involvement of the hypothalamus[2], dentate nucleus[2],[4],[5], basal nuclei[2],[4],[5] and cerebellar nuclei[2],[4],[5] have also been reported. TI-weighted imaging reveals these same areas to be mildly hypointense, with no evidence of enhancement following intravenous admini stration of a contrast medium (gadolinium).

These imaging characteristics (Figures 2a/b and 3a/b) are suggestive of cytotoxic oedema – a supposition supported by histopathological examination of a Staffordshire bull terrier[3]. In this latter

case, there were no macroscopic lesions in any organs, with microscopic changes only identified in the brain. Perineuronal and perivascular grey matter astrocytes displayed vacuolation. The contents of these vacuoles were clear and devoid of storage material. Changes also extended into the adjacent white matter, with vacuoles associated with both astrocytes and myelin sheaths, although there was no evidence of debrisfilled macrophages to indicate demyelination[3].

Routine CSF analysis is unremarkable and polymerase chain reaction testing for infectious agents has been unrewarding. However, when performed, elevated levels of L-2-hydroxyglutaric acid and lysine have been detected within CSF[2]. This finding is mirrored by assessment of organic and amino acids in urine, which invariably reveals elevated levels of L-2-hydroxyglutaric acid[2]. The reported levels range from 2,223mmol/mol to 3,922mmol/mol creatinine (with various reference ranges stated, but all between 0.6 and 17). In one dog, high levels of urinary lysine and arginine were also reported to be present, although the full significance of these additional abnormalities and their relation to the clinical disease was unknown[2].

Diagnosis may be confirmed through DNA testing for the mutation at exon 10 of the gene encoding L2HGDH, with affected Staffordshire bull terriers being homozygous for the mutation. Carrier states (heterozygous) have also been documented to be present in close relatives of affected dogs[4],[16]. Since the DNA test was commercially introduced in 2005, 6,474 Staffordshire bull terriers have been tested for this mutation at the Animal Health Trust.

In total over this period, 16 per cent of dogs tested have been either carriers of the mutation or homozygous-affected. Already in 2011, 14 per cent of the dogs tested have been proven to be carriers of the mutation, with three per cent of the dogs affected.

Treatment and prognosis

At present no treatment is available for this condition in humans or dogs. Patients are typically treated with anti-oxidant supplements (L-carnitine, coenzyme Q10) and riboflavin, given the suggestion of oxidative stress as a possible cause of neurodegeneration. This may act to slow the progression of clinical signs, but long-term prognosis is guarded.

Reports have been published in the human literature suggesting a predisposition for patients affected by L-2-HGA to also develop brain tumours[17],[18],[19]. Elevations of L-2-hydroxyglutarate levels have also been reported in cases of papillary thyroid carcinoma[20], and Wilms' tumour[21], calvarial osteoma[22] and spinal canal stenosis[23] have also been proposed to be linked to this condition in humans.

At present, although the population of affected dogs with this condition is likely to be higher than identified in the literature, the numbers of affected cases are relatively small and similar associations to tumour development have not yet been made.

References

- 1. Duran M, Kamerling J P, Bakker H D, van Gennip A H and Wadman S K (1980). L-2-Hydroxyglutaric aciduria: an inborn error of metabolim? *J Inherit Metab Dis* **3**(4): 109-112.
- 2. Abramson C, Platt S R, Jakobs C, Verhoeven N M, Dennis R, Garosi L and Shelton G D (2003). L-2-hydroxyglutaric aciduria in Staffordshire bull terriers, *J Vet Intern Med* **17**: 551-556.
- 3. Scurrell E, Davies E, Baines E, Cherubini G B, Platt S, Blakemore W, Williams A and Schöniger S (2008). Neuropathological findings in a Staffordshire bull terrier with L-2-Hydroxyglutaric aciduria, *J Comp Path* **138**: 160-164.
- 4. Penderis J, Clavin J, Abramson C, Jakobs C, Pettit L, Binns M M, Verhoeven N M, O'Driscoll E, Platt S R and Mellersh C S (2007). L-2-hydroxyglutaric aciduria: characterisation of the molecular defect in a spontaneous canine model, *J Med Genet* **44**: 334-340.
- 5. Garosi L S, Penderis J, McConnell J F and Jakobs C (2005). L-2-hydroxyglutaric aciduria in a West Highland white terrier, *Veterinary Record* **156**: 145-147.
- 6. Sanchez D, Mascort J, Zamora A, Artuch R and Lujan Feliu-Pascual A (2010). L-2 hydroxyglutaric aciduria in a Yorkshire terrier, *Proceedings of the 23rd Annual Symposium of the ECVN and ESVN*.
- 7. Rzem R, Veiga-da-Cunha, Noël G, Goffette S, Nassogne M-C, Tabarki B, Schöller, Marquardt T, Vikkula M and Van Schaftingen E (2004). A gene encoding a putative FAD-dependent L-2-hydroxyglutarate dehydrogenase is mutated in L-2-hydroxyglutaric aciduria, *Proc Natl Acad Sci USA* **101**: 16,849-16,854.
- 8. Topçu M, Jobard F, Halliez S, Coskun T, Yalçinkayal C, Gerceker F O, Wanders R J A, Prud'homme J F, Lathrop M, Özguc M and Fischer J (2004). L-2-hydroxyglutaric aciduria: identification of a mutant gene C14orf160, localized on chromosome 14q22.1, *Hum Mol Genet* **13**: 2,803-2,811.
- 9. Latini A, Scussiato K, Rosa R B, Leipnitz G, Llesuy S, Belló-Klein A, Dutra-Filho C S and Wajner M (2003). Induction of oxidative stress by L-2-hydroxyglutaric acid in rat brain, *J Neurosci Res* **74**(1): 103-110.
- 10. da Silva C G, Bueno A R, Schuck P F, Leipnitz G, Ribeiro C A, Wannmacher C M, Wyse AT and Wajner M (2003). L-2-hydroxyglutaric aciduria inhibits mitochondrial creatine kinase activity from cerebellum of developing rats, *Int J Dev Neurosci* **21**(4): 217-224.
- 11. Karatas H, Saygi S, Bastan B, Eker A, Kursun O, Ayhan Y and Ciger A (2010). L-2-hydroxyglutaric aciduria: report of four Turkish adult patients, *Neurologist* **16**(1): 44-46.
- 12. Goffette S M, Duprez T P, Nassogne M C, Vincent M F, Jakobs C and Sindic C J (2006). L-2-Hydroxyglutaric aciduria: clinical, genetic, and brain MRI characteristics in two adult sisters, *Eur J Neurol* **13**(5): 499-504.
- 13. Topçu M, Aydin O F, Yalçinkaya C, Halilog¢lu G, Aysun S, Anlar B, Topalog¢lu H, Turanli G, Yalnizog¢lu D, Kesimer M and Coskun T (2005). L-2-hydroxyglutaric aciduria: a report of 29 patients, *Turk J Pediatr* **47**(1): 1-7.

- 14. Chen E, Nyhan W L, Jakobs C, Greco C M, Barkovich A J, Cox V A and Packman S (1996). L-2-Hydroxyglutaric aciduria: neuropathological correlations and first report of severe neurodegenerative disease and neonatal death, *J Inherit Metab Dis* **19**(3): 335-343.
- 15. Jequier Gyax M, Roulet-Perez E, Meagher-Villemure K, Jakobs C, Salomons G S, Boulat O, Superti-Furga A, Ballhausen D and Bonafé L (2009). Sudden unexpected death in an infant with L-2-hydroxyglutaric aciduria, *Eur J Pediatr* **168**(8): 957-962.
- 16. www.aht.org.uk/genetics_tests.Html
- 17. Ozis¸ik P A, Akalan N, Palaog¢lu S and Topçu M (2002). Medulloblastoma in a child with the metabolic disease L-2-hydroxyglutaric aciduria, *Pediatr Neurosurg* **37**(1): 22-26.
- 18. Moroni I, Bugiani M, D'Incerti L, Maccagnano C, Rimoldi M, Bissola L, Pollo B, Finocchiaro G and Uziel G (2004). L-2-hydroxyglutaric aciduria and brain malignant tumors: a predisposing condition? *Neurology* **62**(10): 1,882-1,884.
- 19. Aghili M, Zahedi F and Rafiee E (2009). Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review, *J Neuro-oncol* **91**(2): 233-236.
- 20. Rakheja D, Boriack R L, Mitui M, Khokhar S, Holt S A and Kapur P (2011). Papillary thyroid carcinoma shows elevated levels of 2-hydroxyglutarate, *Tumour Biol* **32**(2): 325-333.
- 21. Rogers R E, Deberardinis R J, Klesse L J, Boriack R L, Magraf L R and Rakheja D (2010). Wilms' tumor in a child with L-2-hydroxyglutaric aciduria, *Pediatr Dev Pathol* **13**(5): 408-411.
- 22. Larnaout A, Amouri R, Neji S, Zouari M, Kaabachi N and Hentati F (2007). Osteoma of the calvaria in L-2-hydroxyglutaric aciduria, *J Inherit Metab Dis* **30**(6): 980.
- 23. Warmuth-Metz M, Becker G, Bendszus M and Solymosi L (2000). Spinal canal stenosis in L-2-hydroxyglutaric aciduria, *Arch Neurol* **57**(11): 1,635-1,637.