

## Paper

# A presumptive case of gluten sensitivity in a border terrier: a multisystem disorder?

M. Lowrie, M. Hadjivassiliou, D. S. Sanders, O. A. Garden

**Paroxysmal gluten-sensitive dyskinesia (previously termed canine epileptoid cramping syndrome) is a condition of Border terriers in which the leading manifestation is neurological. The authors describe a case they believe to represent the first report of a Border terrier with a combination of neurological signs, atopy, positive serological results for anti-transglutaminase 2 (TG2 IgA) and anti-gliadin (AGA IgG) antibodies, and signs suggestive of gastrointestinal disease with pathological changes in the gastrointestinal tract—seemingly responsive to a gluten-free diet. As such, the authors suggest that gluten sensitivity in Border terriers may manifest as a multisystem disease in a similar manner to that seen in human beings.**

Gluten-related disorders (GRDs) include a spectrum of multisystem manifestations occurring as a consequence of an auto-immune reaction to gluten with or without signs of gastrointestinal disease (Sapone and others 2012). Gluten is a protein composite of gliadin and glutenin, present along with starch in wheat. Coeliac disease (CD) or gluten-sensitive enteropathy is a common cause of malabsorption in people and the most well-recognised GRD (Catassi and Fasano, 2008). In genetically predisposed individuals, an immune reaction involving B cells, antibody production and intestinal mucosal T lymphocytes leads to intestinal inflammation (gluten-sensitive enteropathy). An increasing number of patients are being recognised as suffering from gluten sensitivity, complaining of gastrointestinal and extraintestinal symptoms but without evidence of enteropathy. Non-coeliac gluten sensitivity is the term given for this phenomenon (Sapone and others 2012).

Gluten sensitivity in dogs has been largely unrecognised. A gluten-sensitive enteropathy has been described in Irish Setters (Hall and Batt 1990, Garden and others 2000) and, more recently, a paroxysmal gluten-sensitive dyskinesia (PGSD) has been reported in Border terriers (Lowrie and others 2015). PGSD (previously termed ‘canine epileptoid cramping syndrome’) is characterised by circumscribed attacks of disturbed movement without loss of consciousness, superimposed on a background state in which such abnormality is absent. Episodes are seen in dogs as

young as six weeks up to seven years of age (Black and others 2014). PGSD consists of episodes of difficulty walking, ranging from ataxia to a complete inability to stand, tremors and dystonia of the limbs, head and neck. Episodes can last minutes or hours with dogs being normal in between. Up to 50 per cent of dogs are reported to have associated gastrointestinal or dermatological signs (Black and others 2014). The current report describes the first report of a canine gluten sensitivity with presumed multisystem involvement.

## Case history

A two-year six-month-old male neutered Border terrier was presented for evaluation of several strange postprandial episodes, consisting of mild whole-body tremors, licking the lips, staring into space, adopting a praying posture, mild dyskinesia of the limbs and becoming mildly ataxic with slow, purposeless pacing (see online supplementary video 1). These episodes would last several minutes after which it would return to normal. Occasional borborygmi, flatulence, haematochezia and faecal mucus were reported by the owner. Frequency and duration of the abnormal episodes increased progressively over a six-month period with neurological signs increasing in severity. At presentation, the dog exhibited multiple consecutive episodes following eating, but the primary concern of the owner was the gastrointestinal signs.

The referring veterinarian had performed a complete blood cell count and serum chemistry panel, which were unremarkable. A canine-specific pancreatic lipase immunoassay was negative. A bile acid stimulation test, trypsin-like immunoreactivity, folate and cobalamin were also within the respective reference intervals. No abnormalities were detected on urinalysis. A bacterial culture of urine showed no growth. Faecal microscopy and culture were unremarkable. Up to this point, the dog had undergone a number of dietary trials using novel protein sources but with no clinical improvement. Despite varied diets with controlled exposure to many protein sources, all diets had contained gluten. Symptomatic therapy with ranitidine had failed to improve this clinical picture.

When initially examined at the referral hospital, the dog was alert with a body condition score of 4/9. Additional history revealed a lifelong history of chewing the paws and frequent episodes of scratching of the left ear. Ooscopic examination

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**M. Lowrie**, MA, VetMB, MVM, DipECVN, MRCVS, Dovecote Veterinary Hospital, 5 Delven Lane, Castle Donington, Derby DE74 2LJ, UK

**M. Hadjivassiliou**, MBChB, MRCP, FRCP, MD, Department of Neurology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

**D. S. Sanders**, MD, FRCP, FACC, Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

**O. A. Garden**, BSc, BVetMed, PhD, FHEA, MSB, DipACVIM, DipECVIM-CA, Department of Clinical Sciences and Services, Royal Veterinary College, Hatfield, Hertfordshire AL9 7TA, UK

E-mail for correspondence: mark.lowrie@dovecoteveterinaryhospital.co.uk

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revealed left-sided otitis externa. The physical and neurological examination did not reveal abnormalities. Measurement of resting plasma ammonia concentration was within the reference interval. Thoracic radiographs and an abdominal ultrasound examination did not reveal abnormalities. Serum anti-transglutaminase 2<sup>i</sup> (TG2 IgA, 1.007; reference interval 0.129–0.285) and anti-gliadin<sup>ii</sup> (AGA IgG, 0.724; reference interval 0.092–0.162) antibodies were increased compared with previously reported controls (Lowrie and others 2015).

A gastroduodenoscopy revealed a small amount of fluid in the oesophagus but no signs of oesophagitis. There were no gross abnormalities in the stomach or duodenum. Lower gastrointestinal endoscopy revealed erythematous foci in the transverse colon and prominent follicles in the descending colon. The ileoceocolic valve appeared inflamed. Blind biopsies of the ileum were collected. Biopsies were also taken from the oesophagus, stomach, duodenum, ileum, caecum and colon. Histopathological review revealed the surface epithelium of the duodenum and ileum to be intact with villi of normal length on all specimens submitted. Histopathological grading was performed using standard criteria (Day and others 2008). No gastric spiral microorganisms were observed. Gastric cells were mainly tall columnar, with mild increases of up to 10 intraepithelial lymphocytes per stretch of 50 enterocytes. There were mild-to-moderate increases in numbers of lymphocytes and plasma cells in the superficial lamina propria in a few foci (30–60 per stretch of 100 enterocytes) and a mild increase of up to eight eosinophils clustered per 100 enterocytes (see Fig 1). In the propria of the villi in the ileac samples, there were mildly increased numbers of lymphocytes and plasma cells (up to 30 per cent of surface length) at a x40 field (although the ileum is not included in the World Small Animal Veterinary Association histological criteria). Eosinophils were mildly increased at up to 10 per stretch of 100 enterocytes in the lamina propria and there were a few scattered neutrophils. The crypts of the colon were mildly hyperplastic in some areas, with up to 10 lymphocytes and plasma cells between the crypts. Up to 10 eosinophils were present per 100 enterocytes, with some rare scattered neutrophils. The histopathological diagnosis was of a mild-to-moderate gastritis, enteritis and colitis with a lymphocytic, plasmacytic and eosinophilic population.

Based on the history, physical examination and test results, a diagnosis of a gluten-sensitive enteropathy was suspected with dermatological and neurological manifestations. A gluten-free diet<sup>iii</sup> was started with instructions to the owners to avoid all other sources of food.

Over the next 14 days, the owners reported no further abnormal episodes following eating, the signs suggestive of gastrointestinal disease abated and the pruritus completely resolved. Repeated serum titres of AGA (AGA IgG, 0.189; reference interval 0.092–0.162) and TG2 (TG2 IgA, 0.401; reference interval 0.129–0.285) antibodies 12 weeks following the institution of the gluten-free diet were significantly decreased, although both remained above the concentration of normal control dogs.

## Discussion

This is, to the authors' knowledge, the first report of suspected combined intestinal and extraintestinal manifestations of gluten sensitivity in a Border terrier. Although gluten sensitivity resulting in multisystem manifestations is not proven, the evidence is compelling. Serological tests used to confirm the diagnosis of gluten sensitivity in people include AGA and TG2 antibodies (Hadjivassiliou and others 2003, Volta and others 2012). In people, TG2 antibodies are specific for enteropathy but are only found in a third of patients with neurological manifestations (Hadjivassiliou and others 2010, 2014). In order to overcome

these shortcomings, various transglutaminase isoenzymes have been studied. Antibodies to TG2, the autoantigen in CD, are seen with enteropathy. Antibodies to TG3 are associated with dermatitis herpetiformis (Sárdy and others 2002) and antibodies to TG6 are found in the majority of patients with neurological manifestations (Hadjivassiliou and others 2008, Hadjivassiliou and others 2013). The latter two tests are not routinely available.

Accurate prevalence of neurological complications due to gluten sensitivity in people is not known. In patients with established CD, the reported prevalence of neurological complications ranges from 10 per cent to 22.5 per cent (Hadjivassiliou and others 2014). Similarly, in patients with neurological manifestations, gastrointestinal symptoms are only detectable in 10 per cent of the cases, but biopsy evidence of CD can be found in up to one-third (Hadjivassiliou and others 2008). This is true in Border terriers with PGSD where despite a history of chronic diarrhoea and vomiting there were unremarkable histological abnormalities of the small intestine (Lowrie and others 2015).

In this case, the dog had an initial presentation of pruritus that had been present for approximately 18 months and preceded all other clinical signs. The dog later developed mild signs of 'canine epileptoid cramping syndrome' (Black and others 2014) and presented to the referring veterinarian for evaluation of signs relating to a gastrointestinal complaint associated with feeding. When the dog was started on a gluten-free diet, it not only improved the gastrointestinal condition, but also the signs consistent with the neurological and dermatological disease. We cannot exclude that the neurological and dermatological signs may have been caused by malabsorption of a vitamin or essential nutrient. As the inflammatory bowel disease improved, the micronutrient deficiency might have been corrected, improving the neurological signs. However, observations in people and dogs (Ghazal and others 2012, Lowrie and others 2015) contradict this hypothesis whereby a patient may present with



FIG 1: Duodenal mucosa from the dog. There is evidence of alterations in mucosal immune cell populations, which are predominantly lymphocytes and plasma cells. Approximately 10 intraepithelial lymphocytes per 100 enterocytes were identified. H&E, bar, 200 µm

<sup>i</sup>ZEDIRA GmbH, Darmstadt, Germany

<sup>ii</sup>Steffens Biotechnische Analysen GmbH, Ebringen, Germany

<sup>iii</sup>Hypoallergenic Canine Dry, Royal Canin, Camargue, France.

neurological signs in the absence of an enteropathy and improve on a gluten-free diet. A more feasible explanation for the gastrointestinal, neurological and dermatological signs described is an immunological link between the three. The exact mechanism of this relationship between gluten sensitivity and the diverse manifestations is not well established at this time and requires further research to be undertaken.

The presence of a lymphocytic-eosinophilic enteritis should be viewed with caution owing to the apparent discordance between clinical presentation and severity of inflammation and the frequent findings of enteritis in clinically silent dogs (Willard and Mansell, 2011). It is stated that the decision to biopsy should be taken only once therapeutic trials (e.g. dietary, antibiotic, anthelmintic, probiotic) have been performed (Washabau and others 2010). Various food trials had been carefully performed on this dog before investigation was undertaken at the referral hospital. Furthermore, the presence of gastrointestinal inflammation with positive gluten serological test results and the occurrence of signs suggestive of gastrointestinal disease support the notion that gluten can result in an immune-mediated enteropathy, encephalopathy and dermatopathy.

The authors accept that there are a number of limitations in this report. The therapeutic diet given to this dog was selected because it was gluten free. However, inevitably there will be many other differences between this diet and the foodstuffs previously administered. Therefore, any improvement in clinical signs in response to change of diet cannot be attributed just to one component of the diet and hence a direct link to gluten sensitivity is not proven here, although its association with a serological and clinical improvement is strongly supportive of a causal relationship. The serological tests performed in this dog only indicate that an immune response has been mounted to exposure to gliadin and does not confirm that the clinical signs are due to gluten exposure. Furthermore, a reduction in AGA and TG2 antibody concentrations following a change to a gluten-free diet would be expected due to decreased exposure and this change may not be of clinical significance. The only way to conclusively prove a clinical association with gluten would be to rechallenge the dog with gluten to document a recurrence of clinical signs.

## Conclusions

This case report demonstrates the spectrum of clinical multisystem manifestations that may be associated with gluten sensitivity in Border terriers. Recognition of clinical signs suggestive of neurological, gastrointestinal and dermatological disease may aid in the identification of this condition and alert the clinician to the consideration of gluten serological testing. Strict adherence to a gluten-free diet allows a serological response in addition to complete amelioration of all associated clinical signs.

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/vr.103910>).

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