

This is the peer-reviewed, manuscript version of an article published in *Veterinary Record*. The final version is available online at <http://dx.doi.org/10.1136/vr.103910>.

The full details of the published version of the article are as follows:

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

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JOURNAL TITLE: *Veterinary Record*

PUBLISHER: BMJ Publishing Group

PUBLICATION DATE: December 2016

DOI: 10.1136/vr.103910

1 *Case Report*

2 **A PRESUMPTIVE CASE OF GLUTEN SENSITIVITY IN A BORDER TERRIER: A**  
3 **MULTI-SYSTEM DISORDER?**

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20 **Running Title:** Gluten Related Disorders

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22 **Keywords:** Dyskinesia, Neurology, Atopy, Inflammatory bowel disease, Dermatology

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24 **Conflict of Interests Statement:** None of the other authors of this paper has a financial or  
25 personal relationship with other people or organizations that could inappropriately influence or  
26 bias the content of this paper

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28 **Word Count:** 1640

29 **Summary**

30           Paroxysmal gluten-sensitive dyskinesia (PGSD; previously termed canine epileptoid  
31 cramping syndrome) is a condition of Border terriers in which the leading manifestation is  
32 neurological. We describe a case we believe to represent the first report of a Border terrier  
33 with a combination of neurological signs, atopy, positive serological results for anti-  
34 transglutaminase 2 (TG2 IgA) and anti-gliadin (AGA IgG) antibodies, and signs suggestive of  
35 gastrointestinal disease with pathological changes in the gastrointestinal tract - seemingly  
36 responsive to a gluten-free diet. As such we suggest that gluten sensitivity in Border terriers  
37 may manifest as a multisystem disease in a similar manner to that seen in humans.

38

39 ***Words 95***

40

## 41 **Introduction**

42           Gluten related disorders (GRD) include a spectrum of multisystem manifestations  
43 occurring as a consequence of an autoimmune reaction to gluten with or without signs of  
44 gastrointestinal disease (Sapone et al., 2012). Gluten is a protein composite of gliadin and  
45 glutenin, present along with starch in wheat. Coeliac disease (CD) or gluten sensitive  
46 enteropathy is a common cause of malabsorption in people and the most well recognised  
47 GRD (Catassi and Fasano, 2013). In genetically predisposed individuals, an immune reaction  
48 involving B cells, antibody production and intestinal mucosal T-lymphocytes, leads to  
49 intestinal inflammation (gluten sensitive enteropathy). An increasing number of patients are  
50 being recognised as suffering from gluten sensitivity, complaining of gastrointestinal and  
51 extra intestinal symptoms but without evidence of enteropathy. Non-coeliac gluten sensitivity  
52 (NCGS) is the term given for this phenomenon (Sapone et al., 2012).

53  
54           Gluten sensitivity in dogs has been largely unrecognized. A gluten sensitive  
55 enteropathy has been described in Irish Setters (Hall and Batt 1990; Garden et al., 2000) and  
56 more recently a paroxysmal gluten-sensitive dyskinesia (PGSD) has been reported in Border  
57 terriers (Lowrie et al., 2015). Paroxysmal gluten-sensitive dyskinesia (previously termed  
58 ‘canine epileptoid cramping syndrome’) is characterised by circumscribed attacks of disturbed  
59 movement without loss of consciousness, superimposed on a background state in which such  
60 abnormality is absent. Episodes are seen in dogs as young as 6 weeks up to 7 years of age  
61 (Black et al., 2014). PGSD consists of episodes of difficulty walking, ranging from ataxia to a  
62 complete inability to stand, tremors, and dystonia of the limbs, head and neck. Episodes can  
63 last minutes or hours with dogs being normal in between. Up to 50% of dogs are reported to  
64 have associated gastrointestinal or dermatological signs (Black et al., 2014).

65

66           The current report describes the first report of a canine gluten sensitivity with  
67 presumed multi-system involvement.

68

### 69 **Case History**

70           A 2-year 6-month-old male neutered Border terrier was presented for evaluation of  
71 several strange post-prandial episodes, consisting of mild whole body tremors, licking the  
72 lips, staring into space, adopting a praying posture, mild dyskinesia of the limbs and  
73 becoming mildly ataxic with slow, purposeless pacing (see Video 1). These episodes would  
74 last several minutes after which he would return to normal. Occasional borborygmi,  
75 flatulence, haematochezia and faecal mucus were reported by the owner. Frequency and  
76 duration of the abnormal episodes increased progressively over a 6-month period with  
77 neurological signs increasing in severity. At presentation, the dog exhibited multiple  
78 consecutive episodes following eating, but the primary concern of the owner was the  
79 gastrointestinal signs.

80

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

90

91           When initially examined at the referral hospital, the dog was alert with a body  
92 condition score of 4/9. Additional history revealed a life-long history of chewing the paws  
93 and frequent episodes of scratching of the left ear. Ooscopic examination revealed left sided  
94 otitis externa. The physical and neurological examination did not reveal abnormalities.  
95 Measurement of resting plasma ammonia concentration was within the reference interval.  
96 Thoracic radiographs and an abdominal ultrasound examination did not reveal abnormalities.  
97 Serum anti-transglutaminase 2<sup>a</sup> (TG2 IgA, 1.007; reference interval 0.129-0.285) and anti-  
98 gliadin<sup>b</sup> (AGA IgG, 0.724; reference interval 0.092-0.162) antibodies were increased  
99 compared to previously reported controls (Lowrie et al., 2015).

100

101           A gastroduodenoscopy revealed a small amount of fluid in the oesophagus but no  
102 signs of oesophagitis. There were no gross abnormalities in the stomach or duodenum. Lower  
103 gastrointestinal endoscopy revealed erythematous foci in the transverse colon and prominent  
104 follicles in the descending colon. The ileocecolic valve appeared inflamed. Blind biopsies  
105 of the ileum were collected. Biopsies were also taken from the oesophagus, stomach,  
106 duodenum, ileum, caecum and colon. Histopathological review revealed the surface  
107 epithelium of the duodenum and ileum to be intact with villi of normal length on all  
108 specimens submitted. Histopathological grading was performed using standard criteria (Day  
109 et al., 2008). No gastric spiral microorganisms were observed. Gastric cells were mainly tall  
110 columnar, with mild increases of up to 10 intraepithelial lymphocytes per stretch of 50  
111 enterocytes. There were mild to moderate increases in numbers of lymphocytes and plasma  
112 cells in the superficial lamina propria in a few foci (30-60 per stretch of 100 enterocytes) and  
113 a mild increase of up to eight eosinophils clustered per 100 enterocytes (see figure 1). In the  
114 propria of the villi in the ileac samples there were mildly increased numbers of lymphocytes  
115 and plasma cells (up to 30% of surface length) at a x40 field (although the ileum is not

116 included in the WSAVA histological criteria). Eosinophils were mildly increased at up to 10  
117 per stretch of 100 enterocytes in the lamina propria and there were a few scattered  
118 neutrophils. The crypts of the colon were mildly hyperplastic in some areas, with up to 10  
119 lymphocytes and plasma cells between the crypts. Up to ten eosinophils were present per 100  
120 enterocytes, with some rare scattered neutrophils. The histopathological diagnosis was of a  
121 mild to moderate gastritis, enteritis and colitis with a lymphocytic, plasmocytic and  
122 eosinophilic population.

123

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

127

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

134

## 135 **Discussion**

136         This is, to our knowledge, the first report of suspected combined intestinal and  
137 extraintestinal manifestations of gluten sensitivity in a Border terrier. Although gluten  
138 sensitivity resulting in multi-system manifestations is not proven, the evidence is compelling.  
139 Serological tests used to confirm the diagnosis of gluten sensitivity in people include AGA  
140 and TG2 antibodies (Hadjivassiliou 2003; Volta et al., 2012). In people, TG2 antibodies are



141 specific for enteropathy but are only found in a third of patients with neurological  
142 manifestations (Hadjivassiliou et al., 2010; Hadjivassiliou et al., 2014). In order to overcome  
143 these shortcomings, various transglutaminase isoenzymes have been studied. Antibodies to  
144 TG2, the autoantigen in CD, are seen with enteropathy. Antibodies to TG3 are associated with  
145 dermatitis herpetiformis (Sárdy et al., 2002) and antibodies to TG6 are found in the majority  
146 of patients with neurologic manifestations (Hadjivassiliou 2008; Hadjivassiliou et al., 2013).  
147 The latter two tests are not routinely available.

148

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

157

158         In our case, the dog had an initial presentation of pruritus that had been present for  
159 approximately 18 months and preceded all other clinical signs. The dog later developed mild  
160 signs of ‘canine epileptoid cramping syndrome’ (Black et al., 2014) and presented to the  
161 referring veterinarian for evaluation of signs relating to a gastrointestinal complaint associated  
162 with feeding. When the dog was started on a gluten-free diet, it not only improved the  
163 gastrointestinal condition, but also the signs consistent with the neurological and  
164 dermatological disease. We cannot exclude that the neurological and dermatological signs  
165 may have been caused by malabsorption of a vitamin or essential nutrient. As the

166 inflammatory bowel disease improved, the micronutrient deficiency might have been  
167 corrected, improving the neurological signs. However, observations in people and dogs  
168 (Ghazal et al., 2012; Lowrie et al., 2015) contradict this hypothesis whereby a patient may  
169 present with neurological signs in the absence of an enteropathy and improve on a gluten-free  
170 diet. A more feasible explanation for the gastrointestinal, neurological and dermatological  
171 signs described is an immunological link between the three. The exact mechanism of this  
172 relationship between gluten sensitivity and the diverse manifestations is not well established  
173 at this time and requires further research to be undertaken.

174

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

185

186         We accept that there are a number of limitations in this report. The therapeutic diet  
187 given to this dog was selected because it was gluten free. However, inevitably there will be  
188 many other differences between this diet and the foodstuffs previously administered.  
189 Therefore any improvement in clinical signs in response to change of diet cannot be attributed  
190 just to one component of the diet and hence a direct link to gluten sensitivity is not proven

191 here although its association with a serological and clinical improvement is strongly  
192 supportive of a causal relationship. The serological tests performed in this dog only; indicate  
193 that an immune response has been mounted to exposure to gliadin and does not confirm that  
194 the clinical signs are due to gluten exposure. Furthermore, a reduction in AGA and TG2  
195 antibody concentrations following a change to a gluten-free diet would be expected due to  
196 decreased exposure and this change may not be of clinical significance. The only way to  
197 conclusively prove a clinical association with gluten would be to re-challenge the dog with  
198 gluten to document a recurrence of clinical signs.

199

## 200 **Conclusions**

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

207

## 208 **Conflict of interest statement**

209 None of the authors has any financial or personal relationships that could  
210 inappropriately influence or bias the content of the paper.

211

## 212 **Footnotes**

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## 280 **Videos**

281

282 **Video 1** – A 2-year 6-month-old male neutered Border terrier exhibiting a post-prandial episode  
283 of whole body mild tremors, licking the lips, staring into space, adopting a preying posture,  
284 mild dyskinesia of the limbs and mild ataxia with slow, purposeless pacing.

285

286 **Figures**

287

288 **Figure 1** – Duodenal mucosa from the dog. There is evidence of alterations in mucosal immune  
289 cell populations, which are predominantly lymphocytes and plasma cells. Approximately 10  
290 intraepithelial lymphocytes per 100 enterocytes were identified. Haematoxylin and eosin. Bar,  
291 200µm.



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